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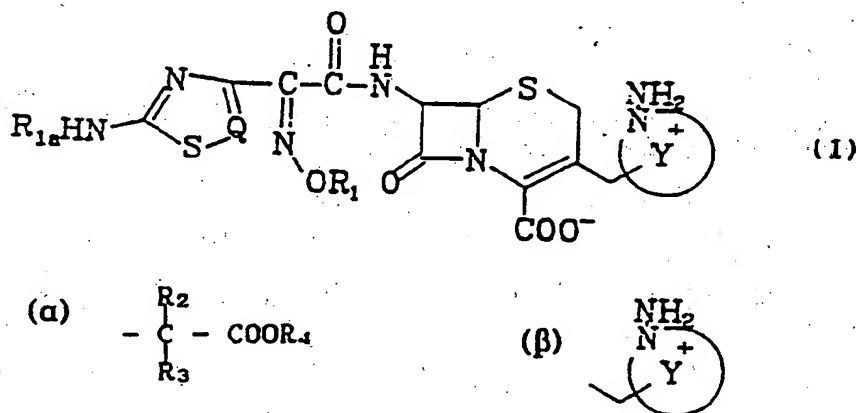
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(54) Title: NOVEL 3-SUBSTITUTED CEPHEM COMPOUNDS AND PROCESSES FOR PREPARATION THEREOF



(57) Abstract

The present invention relates to novel cephalosporins of formula (I), wherein R_1 represents a $C_1 \sim C_4$ alkyl group or (a), wherein R_2 and R_3 , independently, represent hydrogen or a $C_1 \sim C_3$ alkyl group and R_4 represents hydrogen or a $C_1 \sim C_4$ alkyl group; R_{1a} represents hydrogen or an amino-protecting group; Q represents CH or N; and formula (b) represents a saturated or unsaturated heterocyclic group which contains 1 to 4 nitrogen atoms of which one is substituted with an amino group to form quaternary ammonium, and oxygen or sulfur, or a fused heterocyclic group thereof formed together with a substituted or unsubstituted benzene or an optional heterocyclic group, or a pharmaceutically acceptable salt thereof, to processes for preparing the same and to a pharmaceutical composition containing the same as an active ingredient. The compounds (I) according to the invention exhibit potent antibacterial activity and broad antibacterial spectrum against the Gram-positive strains including *Staphylococcus* as well as Gram-negative strains including *Pseudomonas*, and, therefore, are expected to be very useful in treatment of various diseases caused by bacterial infection in human beings and animals.

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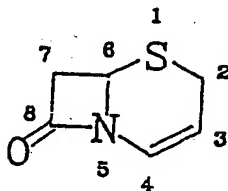
NOVEL 3-SUBSTITUTED CEPHEM COMPOUNDS AND
PROCESSES FOR PREPARATION THEREOF

Field of the Invention

5 The present invention relates to novel cephalosporins and pharmaceutically acceptable salts thereof, which are useful as antibacterial agents. The invention also relates to processes for the preparation of the same, to a pharmaceutical composition containing at least one of the same as active ingredients and to a use of the same for
10 treatment of diseases caused by bacterial infection in human beings and animals.

Background of the Invention

Hereto, it has been known that as antibiotics a great variety of
15 cephalosporins having the basic skeleton of the nucleus of the formula(A):



(A)

have effective antibacterial activities and widely used as antimicrobial
25 agents for infectious diseases caused by various Gram positive and Gram negative strains.

A variety of cephalosporins whose 7-position has 2-aminothiazolyl acetamino group substituted with α -oximino group have been known.

Particularly, the following compounds exhibiting strong antibacterial activities against the enterobacteria have been reported: Cefotaxime in USP 4,152,432 and 4,098,888; Cefmenoxime in USP 4,098,888 and 4,476,122; Ceftriaxone in USP 4,327,210; Ceftazidime in USP 4,258,041 and 4,328,453.

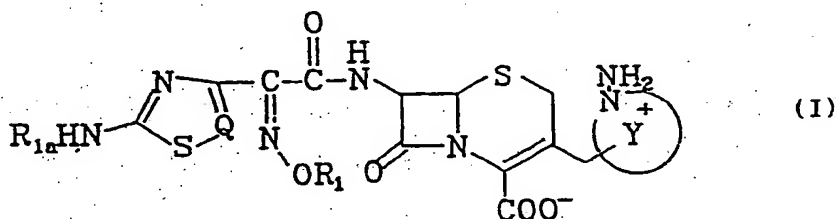
These compounds, however, show relatively weak antibacterial activities against Staphylococcus when compared with Cephaloridine in French Patent No. 1,384,197 or Cefazoline in USP 3,516,997.

Moreover, Ceftazidime exhibits poor antibacterial activity against Staphylococcus, although its antibacterial activity against Pseudomonas is relatively stronger than that of other known cephalosporins.

The present inventors have made intensive researches to prepare cephalosporins having improved antibacterial activities against Staphylococcus with strong antibacterial activities against Pseudomonas. As a result of prolonged studies on numerous cephalosporins, we found the 3-substituted cephem compounds show superior antibacterial activities against both of Staphylococcus and Pseudomonas.

Summary of the Invention

An object of the invention is to provide novel cephalosporins represented by the formula (I):



wherein,

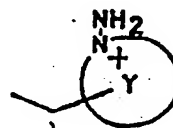
R_1 represents a $C_1 \sim C_4$ alkyl group or $-\overset{\overset{R_2}{|}}{\underset{\underset{R_3}{|}}{C}} - COOR_4$ wherein, R_2

and R_3 , independently, represent hydrogen or a $C_1 \sim C_3$ alkyl group and
 R_4 represents hydrogen or a $C_1 \sim C_4$ alkyl group;

R_1 represents hydrogen or an amino-protecting group;

Q represents CH or N; and

the substituent of the formula



represents a

saturated or unsaturated heterocyclic group containing 1 to 4 nitrogen atoms of which one must be substituted with amino group to form quaternary ammonium, and oxygen or sulfur atoms, or a fused heterocyclic group thereof formed together with a substituted or unsubstituted benzene or optional heterocyclic group,
 and a pharmaceutically acceptable salt thereof.

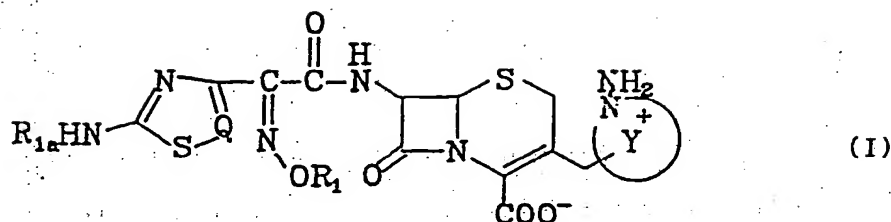
The other object of the invention is to provide processes for preparing the cephalosporins of the formula (I).

The another object of the invention is to provide pharmaceutical compositions containing at least one compound of cephalosporins as active ingredients.

The another object of the invention is to provide a use of cephalosporins of the formula (I) for treatment of the diseases caused by bacterial infection.

Detailed Description of the Invention

The novel cephalosporins according to the invention may be represented by the following formula (I):



wherein,

10 R_1 represents a $C_1 \sim C_4$ alkyl group or $- \overset{\overset{R_2}{|}}{\underset{\underset{R_3}{|}}{C}} - COOR_4$ wherein, R_2 and

R_3 , independently, represent hydrogen or a $C_1 \sim C_3$ alkyl group and R_4 represents hydrogen or a $C_1 \sim C_4$ alkyl group;

R_{1a} represents hydrogen or an amino-protecting group;

Q represents CH or N; and

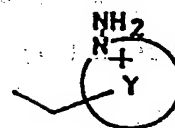
15 the formula



represents a saturated or unsaturated

20 heterocyclic group containing 1 to 4 nitrogen atoms of which one must be substituted with amino group to form quaternary ammonium, and oxygen or sulfur atoms, or a fused heterocyclic group thereof formed together with a substituted or unsubstituted benzene or optional heterocyclic group.

The examples of the 3-position substituent



may include

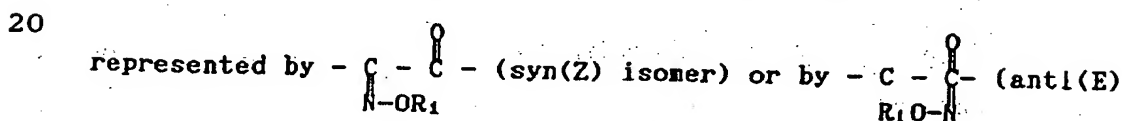
25 1-aminopyrrolidinium methyl,

1-aminopiperidinium methyl,

(4-aminomorpholin-4-ium)methyl,

- (1-amino-1,2,3,6-tetrahydropyridinium)methyl,
 (1-amino-3-pyrrolin-1-ium)methyl,
 1-aminoindolinium methyl,
 1-aminopyrrolium methyl
 5 1-aminoindolium methyl
 (1-amino-4-hydroxypiperidinium)methyl,
 (2-amino-1,2,3,4-tetrahydroisoquinolin-2-ium)methyl,
 (1-amino-1-methyl-4-piperazinium)methyl,
 (4-amino-1,2,4-triazol-2-ium)methyl,
 10 (1-amino-1,2,3-triazol-3-ium)methyl,
 (1-amino-1,2,4-triazol-4-ium)methyl,
 (1-aminobenzotriazol-3-ium)methyl,
 (1-aminobenzimidazol-3-ium)methyl,
 (1-aminoimidazol-3-ium)methyl,
 15 (1-aminopyrazol-2-ium)methyl,
 (1-aminotetrazol-4-ium)methyl,
 (1-amino-1,4,5,6-tetrahydropyrimidin-3-ium)methyl and
 (1-aminoindazol-2-ium)methyl.

The C-7 position of the formula (I) may be



isomer). However, generally, the syn isomer is preferred.

For the present invention, both of the starting materials and the
 25 products are syn isomer.

The pharmaceutically acceptable salts of the compounds (I) are conventional non-toxic salts and may include an inorganic acid salt (e.g., sulfate, hydrochloride, hydrobromide, iodide, phosphate etc.), an

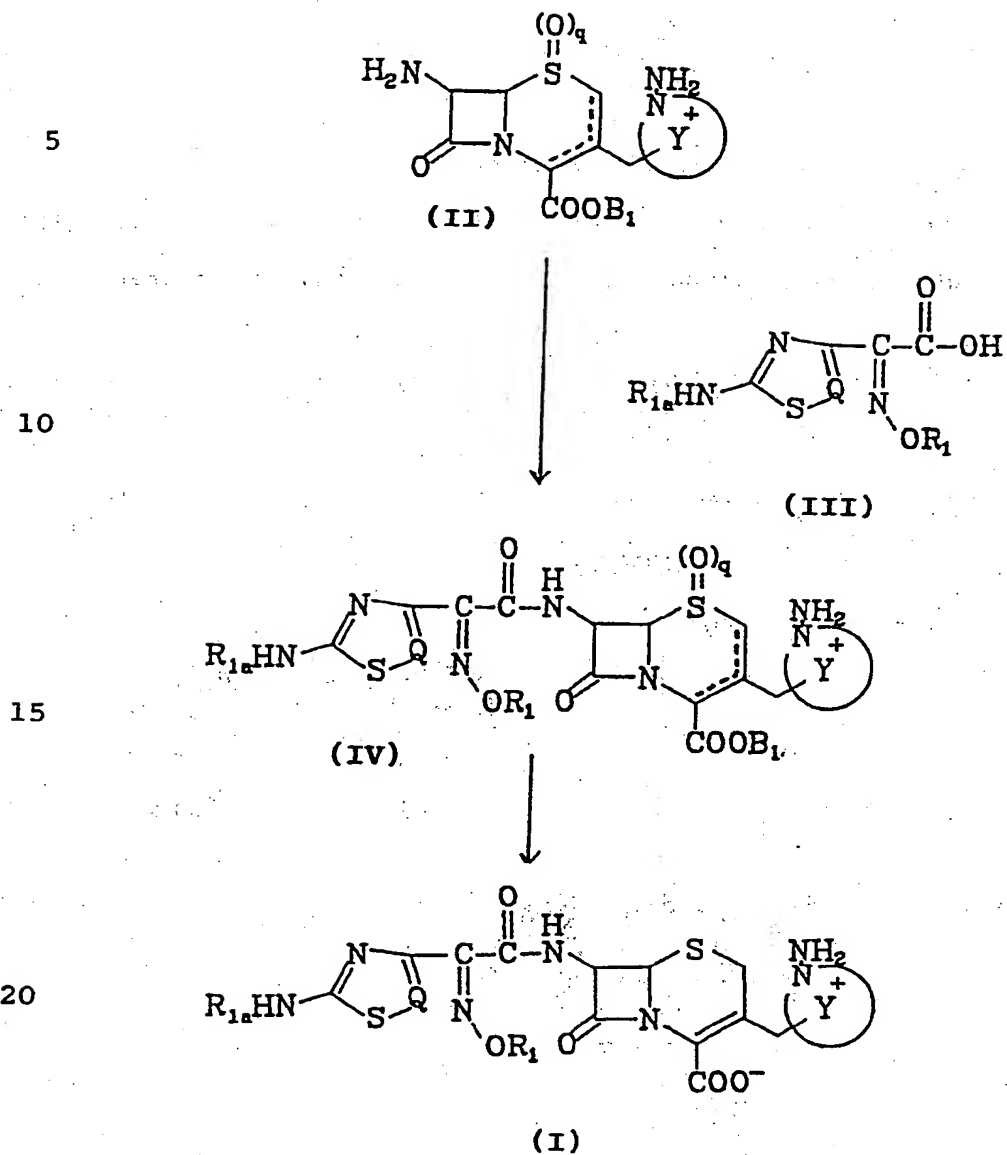
organic carboxylic acid salt (e.g., acetate, maleate, tartrate, fumarate, citrate, succinate, malate, lactate, oxalate, etc.), a sulfonic acid salt (e.g., methanesulfonate, benzenesulfonate, p-toluenesulfonate, etc.), a salt with a basic, or acidic amino acid
5 (e.g., salts with arginine, asparagine, glutamine, lysine, etc.), an inorganic salt, for example, metal salts such as an alkali metal salt (e.g., sodium salt, potassium salt), and an alkaline earth metal salt (e.g. magnesium salt), an ammonium salt, and an organic salt, (e.g., trimethylamine salt, triethylamine salt, pyridine salt, procaine salt,
10 picoline salt, dicyclohexylamine salt, N-methylglucamine salt, diethanolamine salt, triethanolamine salt, phenylethylbenzylamine salt, dibenzylethylenediamine salt, etc.).

For the present invention, an inorganic acid salt such as sulfate or hydrochloride and an organic acid salt such as maleate or fumarate are
15 particularly preferred since they are formed stable crystalline salts of the cephalosporins(I)

According to the present invention, processes for preparing the cephalosporins(I) and pharmaceutically acceptable salts thereof are provided.

20 The cephalosporins according to the invention may be prepared by the following processes:

The First reaction scheme:



Wherein,

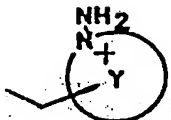
25 R₁ and Q are the same as defined above;

R_{1a} represents hydrogen or an amino-protecting group;

B₁ represents hydrogen or a carboxyl-protecting group;

q represent integer of 0 or 1;

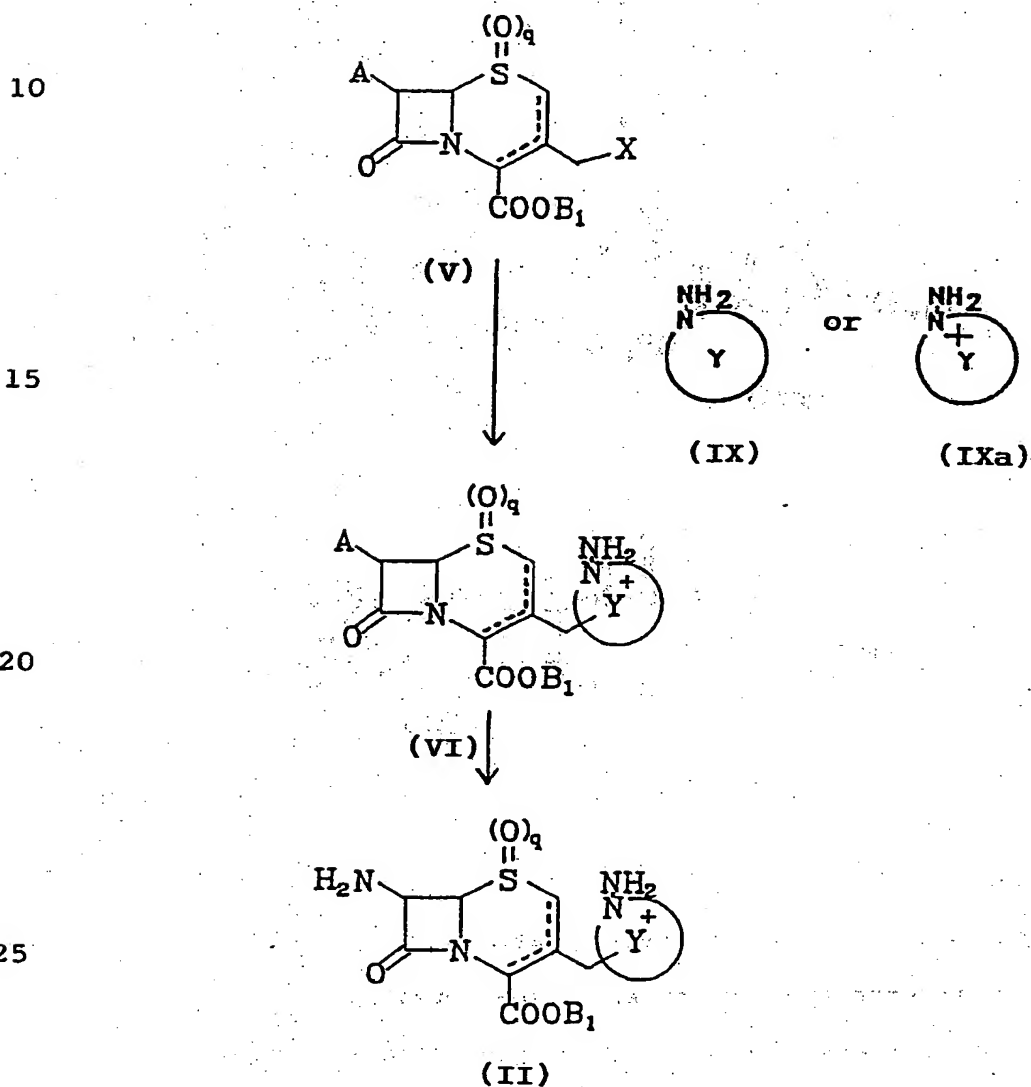
the formula



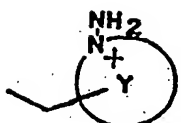
is the same as defined above; and

5 the dotted line means ceph-2-en or ceph-3-en compound.

In the first reaction scheme, the compound of the formula (II) as an intermediate may be synthesized by the following procedure:

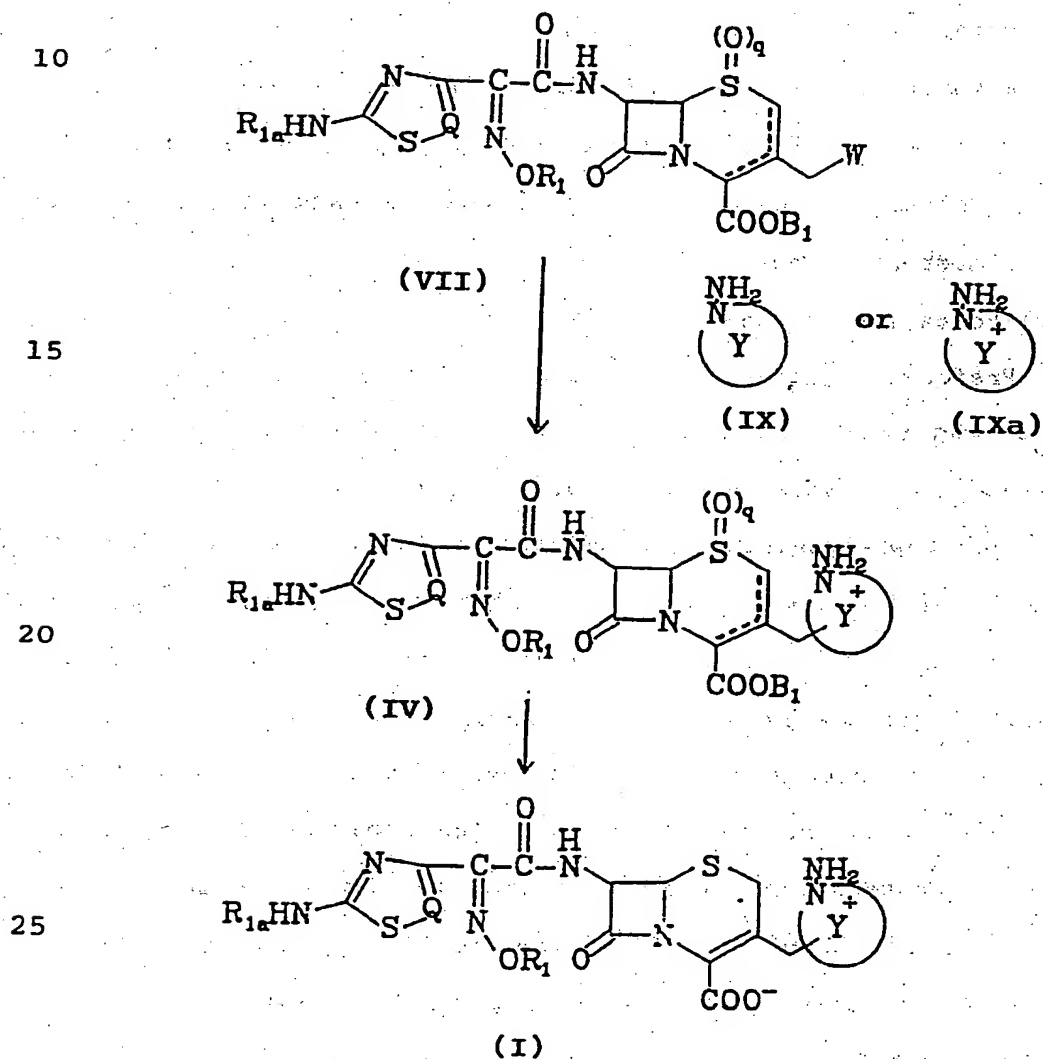


Wherein,

B₁, q,  and the dotted line are the same as defined above;

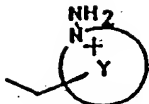
- 5 X represents a leaving group, which is halogen or an acetoxy group; and
 A represents an amine or imine group which are protected by amino protecting groups.

The second reaction scheme:



Wherein,

R_1 , R_{1a} , Q , B_1 , q ,



and the dotted line are the same as

5 defined above; and

W represents a residue which may be substituted with nucleophile.

In preparing the compounds of the formula (I) according to the first or second reaction scheme, any of the following steps can be suitably conducted, if necessary:

- 10 (i) Removing of carboxyl- or amino- protecting group
- (ii) Conversion of Δ^2 isomer to Δ^3 isomer, or vice versa
- (iii) Conversion(Reduction) of sulfoxide compound ($q=1$) to sulfide compound ($q=0$)
- (iv) Formation of non-toxic salt

15 Preferred compounds of the formula (II) and (VII) in the above first or second reaction scheme are those compounds in which q is 0 and the dotted line represents ceph-3-em.

Δ^2 cephalosporin ester derivative ($q=1$) obtained according to the process of the invention may be converted to Δ^3 cephalosporin ester by
 20 treating with base such as triethylamine or pyridine. In case that sulfoxide compound ($q=1$) is obtained, it may be converted to sulfide compound by treating with reducing agent such as sodium dithionite.

The amino- or carboxyl- protecting group may be suitably selected from the conventional protecting groups which are commonly employed in
 25 the technical field of β -lactam and peptide synthesis.

The amino-protecting group may include phthaloyl, formyl, monochloroacetyl, dichloroacetyl, trichloroacetyl, methoxycarbonyl,

ethoxycarbonyl, t-butoxycarbonyl, trichloroethoxycarbonyl, benzyloxycarbonyl, p-nitrobenzyloxycarbonyl, diphenylmethyloxycarbonyl, methoxymethyloxycarbonyl, trityl, trimethylsilyl, phenylacetyl, salicyl, benzoyl and the like.

5 The carboxyl-protecting group may be include t-butyl, t-amyl, benzyl, p-nitrobenzyl, p-methoxybenzyl, benzhydryl, phenyl, p-nitrophenyl, methoxymethyl, ethoxymethyl, benzyloxymethyl, acetoxymethyl, methylthiomethyl, trityl, trichloroethyl, trimethylsilyl, dimethylsilyl, dimethylaminoethyl and the like.

10 The compounds of the formula (II) can be prepared by the method described in Llynn et al., Cephalosporins and penicillin, Academic Press, p 151~171 (1972). For example, they can be prepared by reacting 7 β -acylamino-3-halomethyl-3-cephen-4-carboxylate derivatives disclosed in Japanese Patent Unexamined Publication Nos. 83-72590 or
15 83-154588 with the compounds of the formula (IX) or (IXa).

The compounds of the formula (II) also can be prepared by a conventional method using acids, for example, trifluoroacetic acid, formic acid, conc.hydrochloric acid or phosphorus halide (e.g., phosphorous pentachloride, phosphorus oxychloride, etc.).

20 The acylation in the first reaction scheme is conducted by reacting 1 mole of the compound(II) with 1 to 3 moles of carboxylic reactive derivative of the compound(III).

The examples of the reactive derivatives may include an acid halide, an acid anhydride, an active amide, an active ester and the like.

25 Preferred examples are an acid halide such as acid chloride or acid bromide, a mixed acid anhydride such as acetic acid, pivalic acid, isopivalic acid or trichloroacetic acid, an active amide such as

pyrazole, imidazole, dimethylpyrazole or benzotriazole, and an active ester such as p-nitrophenylester, 2,4-dinitrophenylester, trichlorophenylester, 1-hydroxy-1H-2-pyridone, N-hydroxysuccinimide or N-hydroxyphthalide.

5 The acylation is preferably conducted in the presence of condensing agents in case that the compounds(III) are a free acid form. The examples of the condensing agent may include a carbodiimide compound such as N,N-dicyclohexylcarbodiimide, N-cyclohexyl-N'-morpholinoethyl-carbodiimide, N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide and
10 the like. The acylation also may be conducted in the presence of Vilsmeier reagents formed from the reaction of amide compounds such as N-methylformamide or N,N-dimethylformamide with halides such as thionyl chloride, phosphorus oxychloride or phosgene.

When acid halides or acid anhydrides are used as reactive
15 derivatives, it is necessary to conduct acylation in the presence of acid condensing agents, for example an organic base such as triethylamine, trimethylamine, ethyldiisopropylamine, N,N-dimethylamine, N-methylmorpholine or pyridine, an alkali metal compound such as hydroxide, carbonate or bicarbonate of sodium, potassium or calcium, and
20 oxylan such as ethylene oxide or propylene oxide.

The reaction is carried out in the presence of the solvents which do not influence the reaction adversely. The examples of the solvent may include water, acetone, acetonitrile, dioxane, tetrahydrofuran, dichloromethane, chloroform, dichloroethane, N,N-dimethylformamide or
25 mixtures thereof.

The reaction temperature is not specifically limited, but generally ranges between -30°C and 40°C.

The reaction time generally ranges between 30 min and 10 hours.

The protecting group should be removed in case that the acylated product has a protecting group. The method for removing the protecting group may be suitably selected according to the kind of the protecting group from the methods using an acid, methods using a base or methods using a hydrazine, which are generally used in the field of β -lactam and peptide synthesis.

With regard to the process of the second reaction scheme, the example of the residue W may include an acetoxy group and a halogen atom such as chlorine, bromine or iodine.

The compounds of (VII) wherein Q is N, B₁ is hydrogen and W is an acetoxy group are may be prepared by a method described in The Journal of Antibiotics, Vol. 36(8), 1020(1983).

The reaction of the compounds (VII) wherein W is an acetoxyl group with the compounds (IX) or (IXa) is preferably carried out in the polar solvents, for example, water, phosphate buffer, acetone, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, tetrahydrofuran, dimethylsulfoxide, dioxane, methanol or ethanol and mixtures thereof with water.

The reaction is preferably carried out around the neutral pH.

The reaction temperature is not specifically limited, but is preferably 15°C to about 70°C.

The reaction time varies depending on the reaction conditions, but is generally 1 to 10 hours.

The reaction may be accelerated by adding alkali metal halides, for example, sodium iodide, lithium iodide or potassium iodide to the reaction mixture.

In case that the compounds (VII) wherein W is a halogen are used to prepare the desired compounds (I), the halogen may include chlorine, bromine and iodine. The halide compound are easily prepared by methods in Japanese Patent Unexamined Publication Nos. 81-131,590, 5 83-90,590 and 84-10,593.

The reaction is preferably carried out in the presence of a solvent such as acetone, dichloromethane, acetonitrile, N,N-dimethylformamide or N,N-dimethylacetamide under the non-aqueous condition.

The reaction temperature is preferably 0 to 50°C and the reaction 10 time is generally 1 to 5 hours.

The protecting group can be removed by known methods to give the compounds(I).

The compounds(IX) or (IXa) which will be introduced into 3-position of the cephem nucleus as substituents are commercially available.

15 For example, 1-aminopyrrolidine, 4-aminomorpholine, 1-aminopiperidine and 4-amino-1,2,4-triazole were purchased from Aldrich. They are also may be synthesized by the known methods. For example, 1-aminopyrrole, 1-aminoindole, 1-amino-1,2,3-triazole, 1-aminobenzotriazole, 1-aminobenzimidazole and 1-aminoindazole were prepared by methods 20 described in Flitsch, W. et al., Chem. Ber., 102, 3268 (1969), Masanori, N. et al., Tetrahedron Lett., 461 (1974), Stolle, R. et al., Chem. Ber., 59, 1743 (1926), Campbell, C.D. et al., J. Chem. Soc. Chem. Commun., 742 (1969), Sheng, M.N. et al., J. Org. Chem., 28, 736 (1963) and Sakai, K. et al., J. Org. Chem., 37, 2351 (1972), respectively.

25 Further, for example, 1-amino-1,2,3,6-tetrahydropyridine, 1-amino-3-pyrroline, 1-aminoindoline, 1-aminohydroxypiperidine, 2-amino-1,2,3,4-tetrahydroisoquinoline, 1-amino-1,2,4-triazole, 1-aminoimidazole,

1-aminopyrazole, 1-aminotetrazole and 1-amino-1,4,5,6-tetrahydropyrimidine also may be prepared by the above methods.

Alternatively, they also may be prepared by reacting 1,2,3,6-tetrahydropyridine, pyrroline, indoline, hydroxypiperidine,

5 1,2,3,4-tetrahydroisoquinoline, 1,2,4-triazole, imidazole, pyrazole or tetrazole with hydroxylamine-O-sulfonic acid or chloramine-T in the presence of an inorganic salt in water or a mixed solvent of water and an organic solvent(1:1~3:1). If necessary, they may be separated and purified by silica gel column chromatography.

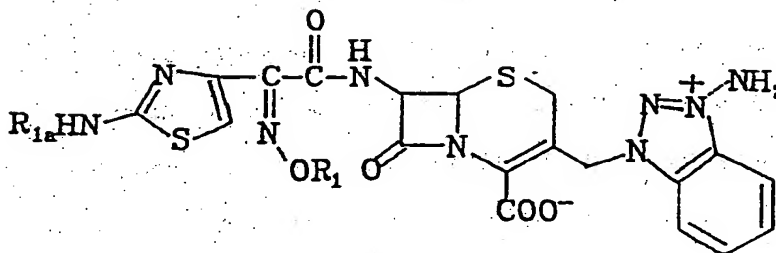
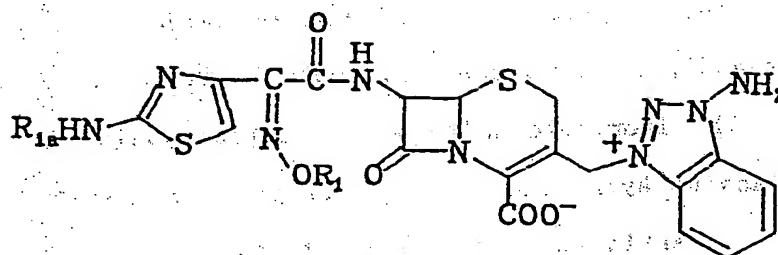
10 The organic solvents are of water-miscible and may be suitably selected from N,N-dimethylformamide, N,N-dimethylformacetamide, methanol, ethanol, acetone, acetonitrile or dioxane.

The inorganic salt may be suitably selected from sodium hydroxide, potassium hydroxide, calcium carbonate or sodium hydride.

15 Particularly, in case that the 3-position substituent is 1-amino-1-methylpiperazinium, the amino group of 1-methylpiperazine is protected by a conventional amino-protecting group, for example, acetyl, benzyloxycarbonyl or t-butoxycarbonyl group. Then, thus obtained amino-protected 1-methylpiperazine is reacted with hydroxylamine-O-sulfonic acid in the presence of an inorganic solvent in water or a
20 mixed solvent of water and an organic solvent to give amino-protected 1-amino-1-methylpiperazinium and the amino-protecting group is deprotected to give the desired compound.

When the heterocyclic compound having two or more nitrogen atoms as
25 a hetero atom, for example, 4-amino-1,2,4-triazole, 1-amino-1,2,3-triazole, 1-amino-1,2,4-triazole, 1-aminopyrazole, 1-aminotetrazole, 1-amino-1,4,5,6-tetrahydropyrimidine,

1-aminobenzotriazole, 1-aminobenzimidazole, 1-aminoindazole or 1-aminoimidazole is introduced into 3-position of the cephem nucleus, the compounds of the formula(I) may exist in tautomeric forms and such tautomers are the equivalent and also included within the scope of the invention. Namely, the position of the positive charge varies depending on the state of salt, the kind of solvent, the properties of solution, the temperature, the kind of substituent and the like, as follows:



The salts of the compounds (I) according to the invention can be prepared by dissolving the compounds of the formula (I) in an aqueous solution of inorganic or organic acid, preferably an aqueous solution containing 1 to 10 equivalents of inorganic or organic acid, stirring

the solution at 0~5°C for 5 to 10 hours, then precipitating to give a crystalline salt of compound (I).

The compounds (I) and salts thereof according to the invention are novel cephalosporins and exhibit potent and broad antibacterial activities against a variety of pathogenic bacteria including Gram-positive and negative strains, particularly against Staphylococcus and Pseudomonas.

In order to illustrate the pharmaceutical usefulness of the compounds (I) of the invention, the representative examples of compounds (I) were tested for their antibacterial activities against the standard test strains and the clinically isolated strains.

The antibacterial activity was determined by an Agar dilution method as described below.

That is, the two-fold serial dilutions of the antibacterial compounds (1000 µg compound/ml) were prepared and dispersed in Muller Hinton Agar in a petri dish to a concentration of 100~0.002 µg/ml. The culture broths of standard test strains were inoculated on the medium to a concentration 10⁷ CFU/ml, and incubated at 37°C for 18 hours. The concentration of compounds (I) at which the strains were not grown was regarded as minimum inhibition concentration (MIC).

The results of antibacterial activity test of the representative examples of the compound (I) against 20 standard test strains shown in terms of MIC were indicated in Table 1.

The MIC of the compound of Example 18 against 254 clinically isolated strains were shown in Table 2.

The representative examples of the compounds (I) according to the invention are as follows:

Compound of Example 1 : (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-aminopyrrolidiniummethyl)-ceph-3-em-4-carboxylate

5 Compound of Example 5 : (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(2-amino-1,2,3,4-tetrahydro-isoquinolin-2-ium)methyl]-ceph-3-em-4-carboxylate

Compound of Example 11 : (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-amino-1-methyl-4-piperazinium)methyl]-ceph-3-em-4-carboxylate

10 Compound of Example 12 : (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(4-amino-1,2,4-triazol-2-ium)methyl]-ceph-3-em-4-carboxylate

Compound of Example 18 : (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-3-em-4-carboxylate

15 Compound of Example 19 : (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-aminobenzimidazol-3-ium)methyl]-ceph-3-em-4-carboxylate

Compound of Example 36 : (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-2-oxymino)acetamido]-3-[(4-amino-1,2,4-triazol-2-ium)methyl]-ceph-3-em-4-carboxylate

20 Compound of Example 85 : (6R,7R)-7-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-3-em-4-carboxylate

25 Cefotaxime-Sodium was used as a control.

20 standard test strains used in the present invention are pathogenic strains causing various infections such as urinary tract

infection, respiratory track infection, dermal soft tissue infection, blood plasma infection, stomach-intestine infection or central nerve system infection, and most of them are β -lactamase producing strains.

They are shown below:

5

Gram-positive bacteria

1. Streptococcus pyogenes A 308
2. Streptococcus pyogenes A 77
3. Streptococcus faecium MD 86
4. Staphylococcus aureus SG 511
5. Staphylococcus aureus 285
6. Staphylococcus aureus 503

10

Gram-negative bacteria

7. Escherichia coli O 55
8. Escherichia coli DC 0
9. Escherichia coli DC 2
10. Escherichia coli TEM
11. Escherichia coli 1507E
12. Pseudomonas aeruginosa 9027
13. Pseudomonas aeruginosa 1592E
14. Pseudomonas aeruginosa 1771
15. Pseudomonas aeruginosa 1771M
16. Salmonella typhimurium
17. Klebsiella oxytoca 1082E
18. Klebsiella aerogenes 1522E
19. Enterobacter cloacae P99
20. Enterobacter cloacae 1321E

15

20

25

Table 1. Antibacterial activity of compounds(I)
against the standard test strains; MIC($\mu\text{g/ml}$)

No. of tested strain	compound (No. of Example)	1	5	11	12	18	19	36	85	Cefotax-ine
5	1	0.025	0.049	0.013	0.007	0.004	0.013	0.098	0.007	0.007
	2	0.025	0.013	0.007	0.007	0.004	0.007	0.049	0.004	0.004
	3	>100	50	>100	>100	>100	>100	25	100	100
	4	6.258	1.563	1.563	1.563	0.391	0.781	1.563	0.391	1.563
10	5	12.5	6.250	12.5	3.125	0.781	0.781	3.125	1.563	1.563
	6	1.563	0.781	0.781	0.781	0.195	0.391	1.563	0.391	0.781
	7	0.195	0.391	0.195	0.025	0.007	0.098	0.195	0.007	0.007
	8	0.195	0.391	0.781	0.098	0.025	0.391	0.781	0.025	0.025
15	9	0.391	0.781	0.781	0.097	0.025	0.391	0.195	0.025	0.013
	10	0.391	0.781	0.391	0.049	0.013	0.391	3.125	0.025	0.025
	11	0.391	0.781	0.781	0.098	0.025	0.391	1.563	0.049	0.025
	12	100	50	50	12.5	3.125	50	6.25	3.125	12.5
20	13	100	50	50	6.25	1.563	25	6.25	3.125	12.5
	14	50	50	25	6.25	1.563	12.5	1.563	1.563	6.25
	15	3.125	1.563	1.563	0.195	0.781	0.781	0.098	1.563	0.098
	16	0.781	0.781	0.391	0.098	0.195	0.195	6.250	0.195	0.025
25	17	12.5	12.5	6.250	1.563	0.049	3.125	100	0.781	0.781
	18	0.195	0.013	0.391	0.049	0.025	0.195	0.781	0.049	0.013
	19	>100	100	100	100	12.5	>100	100	25	100
	20	0.098	0.013	0.195	0.025	0.007	0.195	0.391	0.007	0.013

Table 2. Antibacterial activity of the compound of Example 18 against clinically-isolated strains

Strains(No. of tested)	MIC(μ g/ml)		
	Range	50%	90%
5 Enterobacter cloacae (20)	0.007 - 12.5	0.025	0.391
Escherichia coli (20)	0.007 - 0.195	0.013	0.025
Serratia spp (20)	0.013 - 0.098	0.025	0.049
D Streptococcus I (20)	3.125 - 100	12.5	100
D Streptococcus II (20)	3.125 - 100	25	50
Pseudomonas aeruginosa (20)	1.563 - 25	6.25	12.5
Pseudomonas I (19)	0.195 - 12.5	1.563	6.25
Pseudomonas II (19)	0.391 - 12.5	1.563	6.25
Streptococcus I (20)	0.004 - 12.5	0.025	6.25
10 Streptococcus II (17)	0.002 - 0.013	0.004	0.007
Enterococcus I (20)	0.007 - 0.195	0.025	0.049
Enterococcus II (20)	0.004 - 25	0.025	0.098
Morganella morganii (5)	0.004 - 0.025	0.013	0.025
Providencia rettgeri (6)	0.007 - 0.195	0.025	0.098
Proteus mirabilis (4)	0.013 - 0.098	0.013	0.098
Proteus vulgaris (5)	0.025 - 0.195	0.098	0.195

As shown in Table 1, the compounds(I) of the invention exhibit broader antibacterial spectrum and more potent antibacterial activity against Gram-negative and positive strains in comparison with Cefotaxime-Sodium. Particularly, the compound of Example 18 exhibits superior activity against β -lactamase producing strains such as Pseudomonas aeruginosa and Enterobacter cloacae which have clinical problems in the field of cephem antibiotics as well as show strong activity against Gram-positive strains, for example, Staphylococcus aureus which is resistant to the third-generation cephalosporins.

The compounds of Examples 1, 5, 11, 12, 19 and 36 also exhibited excellent antibacterial activity against Gram-positive strains as well as against Gram-negative strains including Pseudomonas.

Particularly, the compounds of Examples 12, 18, 36 and 85 are

expected to be very useful for treatment of an intractable infection diseases caused by Staphylococcus or Pseudomonas.

In order to establish the usefulness in clinical applications of the compounds provided by the invention, the compound of Example 18 was tested for stability against the β -lactamase and for antibacterial activity on systemic infection model.

First, the stability against the β -lactamase was tested by determining the relative(percentage) hydrolysis of the compound of Example 18, relative to that of Cephaloridine, taking the absolute rate of Cephaloridine as 100.

The β -lactamases employed in the test were directly isolated from Enterobacter cloacae P99, E.coli TEM and Citrobacter freundii, and the antibiotics for comparison were Cephaloridine, Cephadrine, Cefoperazone and Cefotaxime.

Cephaloridine, other know antibiotics and the compound of Example 18 were reacted with each of the enzymes isolated from the strains and the OD were determined at 260nm, λ_{max} of Cephaloridine. The relative hydrolysis of various compounds were calculated relative to the OD of Cephaloridine. The results were shown in Table 3.

Table 3. Relative hydrolysis by β -lactamase

Antibiotics (100 μ M) \ Source of β -lactamase	Enterobacter cloacae P99	E. coli TEM	Citrobacter freundii
Cephaloridine	100	100	100
Cephadrine	14.9	0.8	13.6
Cefoperazone	1.4	38.6	1.2
Cefotaxime	0.0	0.6	0.6
Compound of Example 18	0.0	0.0	0.2

The antibacterial activity test on systemic infection model was carried out using the compound of Example 18 as follows: 0.3ml of diluted solution containing lethal dose of strain was administered intraperitoneally to the test animal, and then 5 to 0.078 mg/kg of compound was administered intramuscularly. The PD₅₀ was calculated by T probit method and the result was shown in Table 4.

Table 4. Treatment effect on systemic infection model

Tested strain	PD ₅₀ (mg/kg) (The limit of confidence)*
Streptococcus pyogenes 77A	0.27 (0.08~0.47)

* P < 0.05

Further, in order to illustrate the usefulness of the compounds (I) as a drug, compounds of Examples 12, 18 and 36 were tested for acute toxicity by using 4 weeks-old male ICR-mouse as a test animal.

The compounds were dissolved in physiological saline and phosphate buffered solution (pH 7.0), or if they were not soluble, suspended in carboxymethylcellulose or gum Arabic and then mixed with phosphate buffered solution.

The solution or mixture was administered to the tested animals intravenously or subcutaneously and, after 1 week, the number of surviving animals was calculated.

The results of the acute toxicity test were shown in Table 5.

Table 5. Acute toxicity test

Compound (No. of Example)	LD ₅₀ mg/kg	
	Intravenous administration	Subcutaneous administration
12	> 4000	> 6000
18	> 4000	> 6000
36	> 4000	> 6000

As shown in the Table 5, the LD₅₀ of the tested compounds are more than 4000 mg/kg when intravenously administered and more than 6000 mg/kg when subcutaneously administered, so that it was demonstrated that their safety as a drug was very high.

As described above, the compounds according to the present invention exhibit potent and broad antibacterial activity against Gram-positive strains as well as Gram-negative strains including Pseudomonas, while its toxicity is very low.

The compounds of the invention may be administered parenterally for treatment of bacterial infection in human beings in a dose of 50~1000mg, preferably 100~500mg per adult, 2~4 times a day, preferably.

The pharmaceutical composition according to the invention contains the compounds (I) as an active ingredient in association with solid or liquid excipients. The excipients may include those one which are commonly employed in the field of antibiotic pharmaceuticals.

The pharmaceutical composition may be formulated into solid formulations, for example, tablet, capsule or powder, or liquid formulations, for example, injection solution, suspension or syrup.

The liquid formulations are preferred.

The present invention will be described in detail with reference to the following examples, but is not limited thereto.

Reference Example 1: Synthesis of 1-amino-1,2,3,6-tetrahydropyridine

To a mixed solvent of water(40ml) and methanol(10ml) was added 11.06g(80mmol) of potassium carbonate, and 3.65ml(40mmol) of 1,2,3,6-tetrahydropyridine and 4.52g(40mmol) of hydroxylamine-O-sulfonic acid were added thereto. The mixture was stirred at room temperature for 4.5 hours and concentrated under the reduced pressure to the half of its original volume. The resulting solid was filtered off and the filtrate was extracted with dichloromethane. The organic layer was treated with anhydrous magnesium sulfate and filtered. The filtrate was concentrated under the reduced pressure and then subjected to chromatography over silica gel using 10% methanol/dichloromethane as an eluent to give 1.77g of the desired compound(45%).

Rf = 0.5 (in 10% methanol/dichloromethane)

NMR (D₂O, δ)

2.12~2.48 (m, 2H), 3.20 (t, 2H)

3.42~5.91 (m, 2H)

Reference Example 2: Synthesis of 1-amino-3-pyrroline

To 20ml of water was added 0.69g(10mmol) of 3-pyrroline and 1.68g(30mmol) of potassium hydroxide was added thereto under stirring. 1.7g(15mmol) of hydroxylamine-O-sulfonic acid was added while cooling the mixture to 5°C or below. The reaction mixture was stirred at 40~50°C for 3 hours, cooled and the pH was adjusted to 7~8. Then, it was concentrated under the reduced pressure to remove water.

To the residue was added methanol. After stirring for 10 min, the solid was filtered off and the filtrate was dried over anhydrous magnesium sulfate.

Concentration under the reduced pressure gave 0.4g of the desired compound(17%).

Rf = 0.5 (in 10% methanol/dichloromethane)

NMR (DMSO-d₆, δ)

5 2.72~4.21 (br, 2H, NH₂), 4.54(s, 4H)

5.92 (s, 2H)

Reference Example 3: Synthesis of 1-aminoindoline

In 40ml of water was dissolved 2.76g(20mmol) of potassium carbonate
10 thoroughly, and 10ml of acetonitrile and 2.24ml(20mmol) of indoline were
added thereto in this order. After stirring the reaction mixture for 10
min, 2.26g(20mmol) of hydroxylamine-O-sulfonic acid was added thereto.
After stirring at room temperature for 1.5 hours, the reaction mixture
was concentrated under the reduced pressure. The concentrate was
15 extracted with dichloromethane and treated with anhydrous magnesium
sulfate. After filtration, the filtrate was concentrated under the
reduced pressure, and the resulting concentrate was subjected to
chromatography over silica gel using dichloromethane as an eluent. The
fractions were concentrated to give 0.99g of the desired compound(37%).

20 Rf = 0.17 (in dichloromethane)

NMR (DMSO-d₆, δ)

2.73~3.06 (m, 2H, -CH₂-), 3.25~3.68 (m, 2H, NH₂)

4.10~6.3 (br, 2H, N-CH₂-), 6.71~7.01 (m, 2H)

7.02~7.29 (m, 2H)

25

Reference Example 4: Synthesis of 1-aminoindole

To 50ml of N,N-dimethylformamide were added 24.55g(440mmol) of

potassium hydroxide and 3.201g(27.3mmol) of 1H-indole, and 6.15g (54.4mmol) of hydroxylamine-O-sulfonic acid was added thereto in small amounts under stirring.

After stirring the reaction mixture at room temperature for 1 hour, 50ml of water was added thereto and it was extracted three times with 100ml of benzene. The extract was washed with water, dried and concentrated under the reduced pressure. Silica gel column chromatography of the residue using 50% dichloromethane/n-hexane as an eluent gave 1.16g of the desired compound(32%).

10 n.p. = 41~41.5°C

NMR (CDCl₃, δ)

4.73 (br, 2H, NH₂), 6.37 (d, 1H)

7.01~7.65 (m, 5H, phenyl)

15 Reference Example 5: Synthesis of 1-aminopyrrole

To 10.0g(61.7mmol) of N-aminophthalimide was added a solution of 12ml(72.4mmol) of 2,5-diethoxytetrahydrofuran in 100ml of dioxane and 10ml of 5N hydrochloric acid was added thereto. The reaction mixture was stirred for 1 hour and cooled to 5°C. The resulting precipitate was filtered, recrystallized from dioxane:water(1:3), washed with ethanol and dried to give 10.3g of 1-phthalimidopyrrole. This product was dissolved in 60ml of methanol and 3ml of 82% hydrazine hydrate was slowly added thereto. After refluxing the reaction mixture for 30 min, cooled to 0~5°C and 1.5ml of glacial acetic acid was added thereto. The resulting precipitate was filtered off and the filtrate was concentrated under the reduced pressure to remove methanol. The concentrate was washed with diethyl ether and vacuum-distilled to give

2.4g of the desired compound(47.3%).

bp = 71~73°C (12mmHg)

NMR (CDCl₃, δ)

4.5 (s, 2H, NH₂), 5.89 (t, 2H)

5 6.40 (t, 2H)

Reference Example 6: Synthesis of 1-amino-4-hydroxypiperidine

In 10ml of water was dissolved 0.6g(6mmol) of hydroxylamine-O-sulfonic acid and 1.82g(1.8mmol) of 4-hydroxypiperidine was added thereto. After refluxing for 1 hour, the reaction mixture was cooled to 5°C and 0.84g(6.1mmol) of potassium carbonate was added thereto. The reaction mixture was stirred for 10min and the precipitate was filtered off. The filtrate was concentrated under the reduced pressure and 15ml of dry ethanol was added to give precipitate, which was filtered off. While cooling the filtrate to 5~10°C, 0.85ml of 57% HI was slowly added and the mixture was stirred at the same temperature for 30 min. To the reaction mixture was added 50ml of petroleum ether. The filtrate was washed with acetone to give 1.41g of the desired compound(34%).

20 m.p. = 117~119°C

NMR (DMSO-d₆, δ)

1.12~1.98 (m, 4H), 2.41~2.86 (m, 2H)

2.86~3.24 (m, 2H), 3.40~3.79 (m, 1H)

5.23 (br, 2H, NH₂)

25

Reference Example 7: Synthesis of 2-amino-1,2,3,4-tetrahydroisoquinoline

In a mixed solvent of 50ml of water and 20ml of methanol was

- dissolved 11.06g (80mmol) of potassium carbonate and 5.33g(40mmol) of 1H-1,2,3,4-tetrahydroisoquinoline and 4.52g(40mmol) of hydroxylamine-O-sulfonic acid were added thereto while maintaining the temperature at 30 °C. The mixture was stirred at room temperature for 4 hours. After completion of reaction, the insoluble was filtered off and the filtrate was extracted twice with dichloromethane. The dichloromethane layer was dried over anhydrous magnesium sulfate and concentrated to driness. The resulting residue was subjected to silica gel column chromatography using 5% methanol/dichloromethane as an eluent.
- 10 The fractions containing the desired product were concentrated under the reduced pressure and crystallized from tetrahydrofuran to give 1.78g of the desired compound in a form of white crystal(30%).
- m.p. = 179~181°C
- NMR (DMSO-d₆ + 10% DCl, δ)
- 15 2.95~3.25 (m, 2H, -CH₂-), 3.34~3.64 (m, 2H, N-CH₂-)
4.36 (s, 2H), 7.04~7.32 (m, 4H, phenyl)

Reference Example 8: Synthesis of 1-aminoimidazole.

p-toluenesulfonic acid

- 20 In 50ml of water was dissolved 2.76g(20mmol) of potassium carbonate and 1.36g(20mmol) of imidazole was added thereto. 2.26g(20mmol) of hydroxylamine-O-sulfonic acid was added thereto and the mixture was stirred at room temperature for 6 hours. The resulting precipitate was filtered off and the filtrate was concentrated under the reduced pressure. To the concentrate were slowly added 10ml of chloroform and a solution of 3.8g(20mmol) of p-toluenesulfonic acid monohydrate in 10ml of chloroform. Stirring for 30 min, filtration and drying of the
- 25

mixture gave 1.74g of the desired compound(34%).

NMR (DMSO-d₆, δ)

2.30 (s, 3H, CH₃), 7.26 (m, 4H, phenyl)

7.69 (d, 2H), 9.10 (t, 1H)

5

Reference Example 9: Synthesis of 1-aminopyrazole

p-toluenesulfonic acid

In 500ml of water were dissolved 2.76g(20mmol) of potassium carbonate and 1.31g(20mmol) of pyrazole and 2.26g(20mmol) of hydroxylamine-O-sulfonic acid was added thereto. The reaction mixture was stirred at room temperature for 6 hours and concentrated under the reduced pressure. To the concentrate was added methanol to give precipitate, which was filtered off. After concentrating under the reduced pressure, the concentrate was treated in the same way as Reference Example 8 to give 1.54g of the desired compound(30%).

15

NMR (DMSO-d₆, δ)

2.32 (s, 3H, CH₃), 6.7 (t, 1H)

7.3 (m, 4H, phenyl), 7.65 (d, 2H)

20 Reference Example 10: Synthesis of 1-aminobenzotriazole

In 200ml of water were dissolved 23.83g(0.2mol) of 1H-benzotriazole and 56.11g(1mol) of potassium hydroxide and the solution was maintained at 60°C. To the reaction solution was slowly added 45.2g(0.4mol) of hydroxylamine-O-sulfonic acid over 1 hour while maintaining the temperature at 70~75°C. After completion of addition, the reaction mixture was stirred at 70°C for further 1 hour. After completion of reaction, the reaction solution was cooled to room temperature to

25

precipitate potassium sulfate as crystal, which was filtered off. The filtrate was extracted with dichloromethane (100ml x 5) and the extract was dried over anhydrous magnesium sulfate and concentrated under the reduced pressure to give yellow crystal.

5 Thus obtained crystal was dissolved in 5ml of tetrahydrofuran and the pH was adjusted to 1 with conc.hydrochloric acid to give white crystal.

The filtered crystal was dissolved in 50ml of water and the pH was adjusted to 11~12 with 30% sodium hydroxide followed by extraction with
10 dichloromethane(30mlx4). The extract was dried over anhydrous magnesium sulfate and concentrated under the reduced pressure to give 12.07g of the desired compound(45%).

m.p. = 83~84°C

NMR (CDCl₃, δ)

15 5.80 (br, 2H, NH₂), 7.25~7.55 (m, 2H)
7.70~8.11 (m, 2H)

Reference Example 11: Synthesis of 1-amino-1,2,4-triazole

In 20ml of ethanol was dissolved 14.03g(250mmol) of potassium
20 hydroxide and 3.45g(50mmol) of 1,2,4-triazole was added thereto. The solution of 11.31g(100mmol) of hydroxylamine-O-sulfonic acid in a mixed solvent of water(10ml) and ethanol(10ml) was slowly added to the mixture over 30 min. After stirring at room temperature for 2.5 hours, the resulting precipitate was filtered off and the filtrate was
25 concentrated. To the concentrate was added tetrahydrofuran and the mixture was stirred for 30 min.

The tetrahydrofuran layer was separated, concentrated under the

reduced pressure and diethyl ether was added thereto. The mixture was stirred for 30 min and the diethyl ether layer was separated and concentrated under the reduced pressure. Crystallization of the concentrate from diisopropyl ether/n-hexane gave the 1.63g of the
5 desired compound in a form of crystal(46%).

m.p. = 48~50°C

NMR (DMSO-d₆ + D₂O, δ)

8.58 (s, 1H), 9.36(s, 1H)

10 Reference Example 12: Synthesis of 1-aminoindazole

To a solution of 2.2g(55mmol) of sodium hydroxide in 30ml of water was added 1.33g(10mmol) of 1H-indazole and ethanol was slowly added at 50°C until the reaction mixture was dissolved thoroughly. The resulting mixture was heated to 55°C and 2.83g(25mmol) of
15 hydroxylamine-O-sulfonic acid was slowly added over 30 min with vigorous stirring followed by further stirring for 30 min. After completion of reaction, the resulting precipitate was filtered off, and the filtrate was extracted with dichloromethane(30mlx2), dried over anhydrous magnesium sulfate and concentrated under the reduced pressure.
20 The concentrate was chromatographed over silica gel using 10% ethyl acetate/dichloromethane as an eluent. The fractions containing the desired product were concentrated under the reduced pressure and crystallized from benzene/petroleum ether to give 0.63g of the desired compound(47%).

25 m.p. = 104~106°C

NMR (DMSO-d₆, δ)

5.41 (s, 2H, NH₂), 6.85~7.95 (m, 4H)

8.05 (s, 1H)

Reference Example 13: Synthesis of 1-aminotetrazole

In 125ml of water was dissolved 13.8g(100mmol) of potassium
5 carbonate and 7g(100mmol) of 1H-tetrazole was added thereto. The
reaction solution was heated to 75°C and 11.3g(100mmol) of
hydroxylamine-O-sulfonic acid was slowly added at 70~75°C over 30 min
while adjusting its pH to 7~8. After completion of addition, the
solution was refluxed for 30~35 min, the pH was adjusted to 8 and the
10 solution was extracted with ethyl acetate. The extract was
concentrated under the reduced pressure to give 1.7g of the desired
compound(20%).

b.p. = 153~158°C(2mmHg)

NMR (DMSO-d₆, δ)

15 7.10 (br, 2H, NH₂), 9.12 (s, 1H)

Reference Example 14: Synthesis of 1-amino-1,2,3-triazole

In 20ml of distilled water were dissolved 2.76g(20mmol) of potassium
carbonate and 1.38g(20mmol) of 1H-1,2,3-triazole and 2.26g(20mmol) of
20 hydroxylamine-O-sulfonic acid was added thereto. The mixture was
stirred at room temperature for 9 hours, concentrated under the reduced
pressure and ethanol was added to give a precipitate, which was filtered
off. The filtrate was concentrated under the reduced pressure and
crystallized from tetrahydrofuran/diethyl ether/chloroform to give 0.96g
25 of the desired product(57%).

m.p. = 51°C

NMR (DMSO-d₆ + D₂O, δ)

7.8 (d, 2H)

Reference Example 15: Synthesis of 1-aminobenzimidazole

- In a mixed solvent of water(50ml) and ethanol(50ml) was dissolved
5 19.64g(35mmol) of potassium hydroxide and 5.91g(5mmol) of
1H-benzimidazole was added thereto. Water(10ml) containing 14.41g
(125mmol) of hydroxylamine-O-sulfonic acid was slowly added while
maintaining the temperature at 30°C and the mixture was stirred at the
same temperature for 18 hours.
- 10 The insoluble was filtered off, and the filtrate was extracted with
ethyl acetate. The ethyl acetate layer was dried over anhydrous
magnesium sulfate and concentrated to driness. The concentrate was
subjected to column chromatography over silica gel using 50% ethyl
acetate/dichloromethane as an eluent. The fractions containing the
15 desired product were concentrated under the reduced pressure to give
3.06g of the desired compound in a form of white crystal(46%).

m.p. = 141°C

NMR (DMSO-d₆, δ)

- 6.19 (br, 2H, NH₂), 7.08~7.44 (m, 2H)
20 7.45~7.76 (m, 2H), 8.13 (s, 1H)

Reference Example 16: Synthesis of 1-amino-1,4,5,6-tetrahydropyrimidine

- To 2.76g(20mmol) of potassium carbonate were added 30ml of water and
10ml of ethanol, and 1.64ml(20mmol) of 1H-1,4,5,6-tetrahydropyrimidine
25 was added thereto. Water(10ml) containing 2.26g(20mmol) of
hydroxylamine-O-sulfonic acid was slowly added to the mixture at 30°C or
below and the resulting mixture was stirred at room temperature for 24

hours. After completion of the reaction, the insoluble was filtered off, and the filtrate was extracted twice with ethyl acetate. The ethyl acetate layer containing the desired product was dried over anhydrous magnesium sulfate, concentrated under the reduced pressure and
5 purified by silica gel column chromatography (eluent: 10% aqueous methanol) to give 0.56g of the desired compound(28%).

NMR (DMSO- d_6 , δ)

1.4~1.8 (q, 2H), 3.3~3.8 (n, 4H)

3.6 (s, 1H), 6.5 (br, 2H)

10

Reference Example 17: Synthesis of 1-amino-1-methyl

piperazinium chloride hydrochloride

In 30ml of water was dissolved 2.84g(20mmol) of 4-acetyl-1-methyl piperazine and 3.4g(30mmol) of hydroxylamine-O-sulfonic acid was added
15 thereto. To the mixture, 2.4g(60mmol) of sodium hydroxide was added in small amounts and the resulting mixture was stirred at 40°C for 2 hours, cooled to 5°C and the pH was adjusted to 7~8 with conc.hydrochloric acid while keeping the above temperature. The reaction solution was concentrated under the reduced pressure to remove water and methanol
20 was added to the residue. The mixture was stirred for 1 hour and filtered. The filtrate was dried over anhydrous magnesium sulfate and concentrated under the reduced pressure to give 2.8g of 1-methyl-1-amino-4-acetylpiperazinium in a form of white crystal(88.5%).

Thus obtained product 2.8g(18mmol) was dissolved in 50ml of water
25 and 2.88g (72mmol) of sodium hydroxide was added thereto.

The reaction mixture was stirred at 50°C for 2 hours and the pH was adjusted to 1 with conc.hydrochloric acid. The mixture was

concentrated under the reduced pressure and methanol was added thereto. The resulting mixture was stirred for 1 hour and the precipitate was filtered off. The methanol solution containing the desired product was dried over anhydrous magnesium sulfate and concentrated under the reduced pressure to give 2.33g of the desired compound in a form of white crystal (62%).

m.p. = 230°C (dec.)

NMR (DMSO-d₆, δ)

3.98~3.65 (m, 4H, -CH₂-NH-CH₂), 3.53 (s, 3H, CH₃)

3.75~4.10 (m, 4H), 6.57 (s, 2H, NH₂)

Example 1

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-aminopyrrolidiniummethyl)-ceph-3-em-4-carboxylate

In 40ml of water was dissolved 8.99g(60mmol) of sodium iodide and the solution was heated to 65~70°C. Sodium (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylate(9.54g,20mmol) and 2.94g(24mmol) of 1-aminopyrrolidine hydrochloride were added thereto and the mixture was stirred for 1.5 hours while adjusting its pH to 6~6.5. The reaction solution was cooled to room temperature, its pH was adjusted to 1~1.5 with 3N hydrochloric acid and then was stirred for 30 min. The resulting precipitate was filtered off and the filtrate was concentrated under the reduced pressure and a small amount of water was added thereto. Column chromatography over aluminium oxide(80% aqueous acetonitrile), silica gel(80% aqueous acetonitrile) and then DIAION[®] HP-20(Mitsubishi)(80%

aqueous acetonitrile) were conducted. Concentration followed by lyophilization gave 2.12g of the desired product in a form of white power(22%).

Rf = 0.31 (in 80% aqueous acetonitrile)

5 m.p. = 182°C~(decomp.)

MS (FAB, M+1) = 482

NMR (20% DCI, δ)

1.75~2.30 (m, 4H), 2.90~3.70 (m, 6H)

3.80 (s, 3H, OCH₃), 3.80~4.20 (m, 1H, C-3)

10 4.4~4.9 (m, 1H, C-3), 5.17 (dd, 1H, C-6)

5.7(dd, 1H, C-7), 7.15 (s, 1H, thiazole-H)

Example 2

15 Synthesis of (6R,7R)-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetanido]-3-[(4-aminomorpholin-4-ium) methyl]-ceph-3-em-4-carboxylate

By following the procedure in Example 1 except that 2.31ml(24mmol) of 4-aminomorpholine was employed in place of 1-aminopyrrolidine, there was obtained 2.5g of the desired compound(25%).

20 Rf = 0.35 (in 80% aqueous acetonitrile)

m.p. = 126°C~(decomp.)

NMR (20% DCI, δ)

3.35~4.55 (m, 10H, morpholine, C-2), 4.09 (s, 3H, OCH₃)

4.95~5.34 (q, 2H, C-3), 5.32 (d, 1H, C-6)

25 5.85(d, 1H, C-7), 7.20 (s, 1H, thiazole-H)

Example 3

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-aminopiperidiniummethyl)-ceph-3-em-4-carboxylate

- 5 By following the procedure in Example 1 except that 2.59ml(24mmol) of 1-aminopiperidine was employed in place of 1-aminopyrrolidine, there was obtained 2.3g of the desired product(23%).

Rf = 0.35 (in 80% aqueous acetonitrile)

n.p. = 120°C ~ (decomp.)

- 10 NMR (20% DCl, δ)

1.5~2.2 (m, 6H), 3.75 (s, 3H, OCH₃), 3.2~4.35 (m, 6H)
4.89~5.2 (m, 2H, C-3), 5.37 (d, 1H, C-6)
5.95(d, 1H, C-7), 7.18 (s, 1H, thiazole-H)

15 Example 4

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-amino-4-hydroxypiperidinium)methyl]-ceph-3-em-4-carboxylate

- 20 By following the procedure in Example 1 except that 2.79g(24mmol) of 1-amino-4-hydroxypiperidine was employed in place of 1-aminopyrrolidine, there was obtained 2.1g of the desired product(20%).

Rf = 0.15 (in 80% aqueous acetonitrile)

NMR (20% DCl, δ)

- 25 1.12~1.98 (m, 4H), 3.2~4.4 (m, 7H)
3.85 (s, 3H, OCH₃), 4.86~5.2 (br, 2H, C-3)
5.34(d, 1H, C-6), 5.96 (d, 1H, C-7)
7.2 (s, 1H, thiazole-H)

Example 5

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(2-amino-1,2,3,4-tetrahydroisoquinolin-2-ium)methyl]-ceph-3-em-4-carboxylate

5 In a mixed solvent of acetonitrile(5ml) and water(30ml) was dissolved 4.02g(30mmol) of lithium iodide, 0.99g(6.68mmol) of 2-amino-1,2,3,4-tetrahydroisoquinoline was added thereto and the temperature was raised to 67~70°C. To the reaction solution was added 1.43g(3mmol) of sodium(6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxy-
10 iminoacetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylate, and the reaction mixture was stirred at 70~72°C for 2 hours while adjusting the pH to 6.5~7.0.

After completion of reaction, the reaction solution was cooled to room temperature and stirred for 30 min while adjusting the pH to 1~1.5
15 with 1N hydrochloric acid. The insoluble was filtered off and the filtrate was concentrated under the reduced pressure. The concentrate was subjected to column chromatography over aluminium oxide and silica gel(eluent: 80% aqueous acetonitrile).

The fractions obtained were concentrated under the reduced pressure, and
20 the concentrate was dissolved in a small amount of water followed by purification by DIAION[®] HP-20(Mitsubishi) column chromatography(eluent: 8% aqueous ethanol).

The fractions containing the desired product were concentrated under the reduced pressure and freeze-dried to give 0.23g of the desired compound
25 in a pale yellow amorphous form(14%).

R_f = 0.4 (in 80% aqueous acetonitrile)

MS(FAB, M+1) = 544

NMR (DMSO- d_6 + 20% DCl, δ)

3.1~3.5 (m, 2H), 3.5 ~4.3 (m, 6H)

4.04 (s, 3H, OCH₃), 4.5~5.1 (m, 2H, C-3)

5.2(dd, 1H, C-6), 5.8 (dd, 1H, C-7)

5 7.09 (s, 1H, thiazole-H), 7.1~7.8 (m, 4H, phenyl)

Example 6

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-aminoindoliniummethyl)-ceph-
10 3-em-4-carboxylate

By following the procedure in Example 5 except that 0.9g(6.68mmol) of 1-aminoindoline was employed in place of 2-amino-1,2,3,4-tetrahydroisoquinoline, there was obtained 0.2g of the desired product (13%).

15 Rf = 0.37 (in 80% aqueous acetonitrile)

NMR (DMSO- d_6 + 20% DCl, δ)

2.8~3.1 (m, 2H), 3.4 ~4.4 (m, 4H)

4.01 (s, 3H, OCH₃), 4.6~5.1 (m, 2H, C-3)

5.1(d, 1H, C-6), 5.7 (d, 1H, C-7)

20 7.01 (s, 1H, thiazole-H), 7.03~7.7 (m, 4H, phenyl)

Example 7

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-aminoindoliniummethyl)-
25 ceph-3-em-4-carboxylate

By following the procedure in Example 5 except that 0.9g(6.68mmol) of 1-aminoindole was employed in place of 2-amino-1,2,3,4-

tetrahydroisoquinoline, there was obtained 0.26g of the desired product(17%).

R_f = 0.36 (in 80% aqueous acetonitrile)

NMR (DMSO-d₆ + 20% DCl, δ)

- 5 3.5~3.9 (m, 2H, C-2), 3.86 (s, OCH₃)
4.6~5.1 (m, 2H, C-3), 5.2 (d, 1H, C-6)
5.6(d, 1H, C-7), 6.45 (d, 1H), 7.01 (s, 1H, thiazole-H)
7.05~7.8 (n, 5H, phenyl)

10 Example 8

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-amino-1,2,3,6-tetrahydropyridinium)methyl]-ceph-3-em-4-carboxylate

- In a mixed solvent of acetonitrile(4ml) and water(9ml) was dissolved
15 3.21g(24mmol) of lithium iodide and the solution was heated to 70°C.
0.33g(3.36mmol) of 1-amino-1,2,3,6-tetrahydropyridine was added thereto
and 0.764g(1.6mmol) of sodium (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
methoxyiminoacetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylate was added
while adjusting the pH to 6.5~7. The mixture was stirred at 70~72°C
20 for 1 hour while adjusting the pH to 6.5~7.0.

- The reaction solution was cooled to room temperature, and its pH was
adjusted to 1~1.5 with 3N hydrochloric acid. The solution was stirred
for 30 min, the resulting precipitate was filtered off and the filtrate
was concentrated under the reduced pressure. The concentrate was
25 dissolved in a small amount of water and subjected to column
chromatography over aluminium oxide(80% aqueous acetonitrile), silica
gel(85% aqueous acetonitrile) and DIAION[®] HP-20 (Mitsubishi)(80% aqueous

acetonitrile). The fractions containing the desired product were concentrated and freeze-dried to give 158mg of the desired compound(20%).

Rf = 0.29 (in 80% aqueous acetonitrile)

5 NMR (DMSO-d₆, δ)

2.0~2.4 (m, 2H), 3.0 ~3.9 (m, 6H)

3.97 (s, 3H, OCH₃), 4.0~4.3 (m, 1H, C-3)

4.7~5.1 (m, 1H, C-3), 5.15 (d, 1H, C-6)

5.5~5.9 (m, 3H, C-7), 6.73 (s, 1H, thiazole-H)

10 9.5 (d, 1H, -NH)

Example 9

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-amino-3-pyrrolin-1-ium)methyl]-ceph-3-em-4-carboxylate

15

By following the procedure in Example 8 except that 0.28g(3.36 mmol) of 1-amino-3-pyrroline was employed in place of 1-amino-1,2,3,6-tetrahydropyridine, there was obtained 0.17g of the desired compound (22%).

20 Rf = 0.3 (in 80% aqueous acetonitrile)

NMR (DMSO-d₆ + 20% DCl, δ)

3.6~4.0 (m, 2H, C-2), 3.86 (s, 3H, OCH₃)

4.6 (s, 4H), 4.56~5.1 (m, 2H, C-3)

5.2(d, 1H, C-6), 5.6 (d, 1H, C-7)

25 5.9 (s, 2H), 7.01 (s, 1H, thiazole-H)

Example 10

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-aminopyrrolidinemethyl)-ceph-3-em-4-carboxylate

- 5 By following the procedure in Example 8 except that 0.28g(3.36mmol) of 1-aminopyrrole was employed in place of 1-amino-1,2,3,6-tetrahydropyridine, there was obtained 0.16g of the desired compound(21%).

Rf = 0.29 (in 80% aqueous acetonitrile)

- 10 NMR (DMSO-d₆ + 20% DCl, δ)

3.6~4.1 (m, 2H, C-2), 3.83 (s, 3H, OCH₃)

4.6~5.1 (m, 2H, C-3), 5.15 (d, 1H, C-6)

5.62(d, 1H, C-7), 6.1 (t, 2H)

6.5 (t, 2H), 7.01 (s, 1H, thiazole-H)

15

Example 11

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-amino-1-methyl-4-piperazinium)methyl]-ceph-3-em-4-carboxylate

- 20 In 8ml of water was dissolved 2.5g(17mmol) of sodium iodide, 8ml of acetonitrile was added thereto and the mixture was heated to 65~70°C. 0.376g(2mmol) of 1-amino-1-methylpiperazinium chloride hydrochloride and 0.48g(1mmol) of sodium (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylate were
- 25 added in this order and the pH was adjusted to 6.8 with sodium bicarbonate solution. The reaction solution was stirred at 65~70°C for 2 hours, cooled to room temperature and washed three times with 50ml

of dichloromethane. The aqueous layer was adjusted to pH 2 with 6N hydrochloric acid, concentrated under the reduced pressure and the resulting precipitate was filtered off. The filtrate was concentrated under the reduced pressure and the concentrate was subjected to silica
5 gel column chromatography (80% aqueous acetonitrile). The fractions containing the desired product were purified by HP-20 column chromatography using the same eluent to give 0.37g of the desired compound (73%).

R_f = 0.11 (in 80% aqueous acetonitrile)

10 m.p. = 194°C ~ (decomp.)

MS(FAB, M+1) = 511

NMR (DMSO-d₆, δ)

3.0~3.7 (m, 15H), 3.83 (s, 3H, OCH₃)

4.96 (d, 1H, C-6), 5.51 (dd, 1H, C-7)

15 6.03 (s, 2H, NH₂), 6.73 (s, 1H, thiazole-H)

7.18 (br, 2H), 9.45 (d, 1H, -NH)

Example 12

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(4-amino-1,2,4-triazol-2-ium)methyl]-
20 ceph-3-em-4-carboxylate

In 25ml of distilled water was dissolved 4.3g(30mmol) of sodium iodide and the solution was heated to 70~75°C. 1.0g(12mmol) of 4-amino-1,2,4-triazole and 4.77g(10mmol) of sodium (6R,7R)-7-[(Z)-
25 2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylate were added thereto and the pH was adjusted to 6~6.5. The reaction mixture was stirred at 70~75°C for 1 hour, the reaction

solution was cooled to room temperature and the pH was adjusted to 1~1.5 with 3N hydrochloric acid. The resulting precipitate was filtered off and the filtrate was concentrated under the reduced pressure. The concentrate was dissolved in a small amount of water and subjected to column chromatography over aluminum oxide(80% aqueous acetonitrile) and HP-20 (85% aqueous acetonitrile). The fractions containing the desired product were concentrated and freeze-dried to give 1.68g of the desired product(35%).

Rf = 0.23 (in 80% aqueous acetonitrile)

10 m.p. = 170°C~(decomp.)

MS(FAB, M+1) = 480

NMR (DMSO-d₆ + 20% DCl, δ)

3.3~3.6 (m, 2H, C-2), 3.83 (s, 3H, OCH₃)

5.04 (d, 1H, C-6), 5.0~5.35 (q, 2H, C-3)

15 5.6(d, 1H, C-7), 7.01 (s, 1H, thiazole-H)

8.76, 9.81 (s,s, 2H, triazole)

Example 13

20 Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetanido]-3-[(1-amino-1,2,4-triazol-4-ium)methyl]-ceph-3-em-4-carboxylate

In a mixed solvent of acetonitrile (10ml) and water(10ml) was dissolved 9.69g(64.65 mmol) of sodium iodide and the solution was heated to 70~75°C. 1.63g(19.4mmol) of 1-amino-1,2,4-triazole and 6.17g(12.93 mmol) of sodium (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetanido]-3-acetoxymethyl-ceph-3-em-4-carboxylate were added thereto, and the mixture was stirred at 70~75°C for 1.5 hours while

adjusting the pH to 6~6.5 and cooled to room temperature. After adjusting the pH to 1~1.5 with 3N hydrochloric acid, the reaction mixture was stirred for 30 min. The resulting precipitate was filtered off and the filtrate was concentrated under the reduced pressure. The
5 concentrate was dissolved in a small amount of water and subjected to column chromatography over aluminium oxide (80% aqueous acetonitrile), silica gel (85% aqueous acetonitrile) and then HP-20 (Mitsubishi)(80% aqueous acetonitrile). The fractions containing the desired product were concentrated and freeze-dried to give 2.05g of the desired compound
10 (33%).

R_f = 0.31 (in 80% aqueous acetonitrile)

m.p. = 166°C ~ (decomp.)

MS(FAB, M+1) = 480

NMR (DMSO-d₆ + 20% DCl, δ)

15 3.28~3.7 (m, 2H, C-2), 3.83 (s, 3H, OCH₃)
5.1 (q, 2H, C-3), 5.18 (d, 1H, C-6)
5.61(d, 1H, C-7), 6.91 (s, 1H, thiazole-H)
8.74, 9.68(s,s, 2H, triazole)

20 Example 14

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-aminoimidazol-3-ium)methyl]-ceph-3-em-4-carboxylate

By following the procedure in Example 13 except that 1.61g(19.4mmol)
25 of 1-aminoimidazole was employed in place of 1-amino-1,2,4-triazole, there was obtained 1.95g of the desired compound(32%).

R_f = 0.29 (in 80% aqueous acetonitrile)

NMR (DMSO- d_6 + 20% DCI, δ)

3.2~3.74 (m, 2H, C-2), 3.86 (s, 3H, OCH₃)

5.08 (q, 2H, C-3), 5.2 (d, 1H, C-6)

5.6(d, 1H, C-7), 6.95 (s, 1H, thiazole-H)

5 7.6, 8.3 (s,s, 2H), 9.3 (s, 1H)

Example 15

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-aminopyrazol-2-ium)methyl]-ceph-3-em-4-carboxylate

10

By following the procedure in Example 13 except that 1.61g(19.4mmol) of 1-aminopyrazole was employed in place of 1-amino-1,2,4-triazole, there was obtained 1.81g of the desired compound(29%).

R_f = 0.3 (in 80% aqueous acetonitrile)

15 NMR (DMSO- d_6 + 20% DCI, δ)

3.27~3.74 (m, 2H, C-2), 3.9 (s, 3H, OCH₃)

5.1 (q, 2H, C-3), 5.15 (d, 1H, C-6)

5.68(d, 1H, C-7), 6.7 (t, 1H)

7.02 (s, 1H, thiazole), 7.8, 8.4 (s,s 2H)

20

Example 16

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-aminotetrazol-4-ium)methyl]-ceph-3-em-4-carboxylate

25

By following the procedure in Example 13 except that 1.67g(19.4mmol) of 1-aminotetrazole was employed in place of 1-amino-1,2,4-triazole, there was obtained 1.73g of the desired compound(28%).

Rf = 0.25 (in 80% aqueous acetonitrile)

NMR (DMSO-d₆ + 20% DCl, δ)

3.20~3.74 (m, 2H, C-2), 3.83 (s, 3H, OCH₃)

5.12 (q, 2H, C-3), 5.21 (d, 1H, C-6)

5 5.63(d, 1H, C-7), 7.01 (s, 1H, thiazole-H)

9.7 (s, 1H, tetrazole)

Example 17

10 Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetanido]-3-[(1-amino-1,2,3-triazol-3-ium)methyl]-ceph-3-em-4-carboxylate

By following the procedure in Example 13 except that 1.63g(19.4mmol) of 1-amino-1,2,3-triazole was employed in place of 1-amino-1,2,4-triazole, there was obtained 2.02g of the desired compound(33%).

15 Rf = 0.24 (in 80% aqueous acetonitrile)

m.p. = 126°C ~ (decomp.)

MS(FAB, M+1) = 480

NMR (DMSO-d₆ + 20% DCl, δ)

3.21~3.68 (m, 2H, C-2), 3.9(s, 3H, OCH₃)

20 5.12 (q, 2H, C-3), 5.16 (d, 1H, C-6)

5.65(d, 1H, C-7), 7.01 (s, 1H, thiazole-H)

7.8, 8.7 (s,s, 2H, triazole)

Example 18

25 Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetanido]-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-3-em-4-carboxylate

In a mixed solvent of acetonitrile(10ml) and water(15ml) was dissolved 6.69g(50mmol) of lithium iodide and the solution was heated to 65~67°C. 2.42g(18mmol) of 1-aminobenzotriazole and 4.77g(10mmol) of sodium (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylate were added thereto, and the mixture was stirred at 72°C for 1 hour while adjusting the pH to 6.5~7.0.

After completion of reaction, the reaction solution was cooled to room temperature and stirred for 30 min while adjusting its pH to 1~1.5 with 3N hydrochloric acid. The insoluble was filtered off and the filtrate was concentrated under the reduced pressure. The concentrate was subjected to column chromatography over aluminium oxide and silica gel using 80% aqueous acetonitrile as an eluent. The fractions obtained were concentrated under the reduced pressure and dissolved in a small amount of water. This was purified by HP-20(Mitsubishi) column chromatography (eluent: 15% aqueous acetonitrile). The fractions containing the desired product were concentrated under the reduced pressure and freeze-dried to give 1.48g of the desired compound in pale yellowish white amorphous form (28%).

R_f = 0.3 (in 80% aqueous acetonitrile)

m.p. = 168°C ~ (decomp.)

MS(FAB, M+1) = 530

NMR (DMSO-d₆ + 20% DCl, δ)

3.85~4.0 (m, 2H, C-2), 4.05(s, 3H, OCH₃)

5.05~5.5(q, 2H, C-3), 5.3 (d, 1H, C-6)

5.86(d, 1H, C-7), 7.04 (s, 1H, thiazole-H)

7.65~8.1 (m, 4H, phenyl)

Example 19

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-aminobenzimidazol-3-ium)methyl]-ceph-3-em-4-carboxylate

5 In a mixed solvent of acetonitrile(10ml) and water(20ml) was dissolved 16.06g(120mmol) of lithium iodide, the solution was heated to 65°C and 3.2g(24mmol) of 1-aminobenzimidazole and 5.73g(12mmol) of sodium (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacet-amido]-3-acetoxymethyl-ceph-3-em-4-carboxylate were added thereto. The
10 reaction mixture was stirred at 70°C for 1.5 hours while adjusting the pH to 6.5~7.0.

After completion of reaction, the reaction solution was cooled to room temperature and the pH was adjusted to 1~1.5 with 3N hydrochloric acid. The insoluble was filtered off and the filtrate was concentrated
15 under the reduced pressure.

The concentrate was subjected to column chromatography over aluminium oxide and then silica gel (eluent:80% aqueous acetonitrile). The fractions obtained were concentrated under the reduced pressure and dissolved in a small amount of water. This was purified by HP-20
20 (Mitsubishi) column chromatography using 15% aqueous acetonitrile. The fractions containing the desired product were concentrated under the reduced pressure and freeze-dried to give 2.28g of the desired compound in a white amorphous form(36%).

R_f = 0.3 (in 80% aqueous acetonitrile)

25 m.p. = 155°C ~ (decomp.)

MS(FAB, M+1) = 529

NMR (DMSO-d₆, δ)

3.2~3.7 (m, 2H, C-2), 3.8 (s, 3H, OCH₃)
5.04 (d, 1H, C-6), 5.4~5.8(m, 3H, C-3, C-7)
6.75(s, 1H, thiazole-H), 7.5~8.5 (m, 4H, phenyl)
10.15 (s, 1H, imidazole)

5

Example 20

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-methoxyiminoacetamido]-3-[(1-aminoindazol-2-ium)methyl]-
ceph-3-em-4-carboxylate

10 By following the procedure in Example 19 except that 3.2g(24mmol) of
1-aminoindazole was employed in place of 1-aminobenzimidazole, there was
obtained 1.94g of the desired compound(31%).

Rf = 0.31 (in 80% aqueous acetonitrile)

NMR (DMSO-d₆ + 20% DCl, δ)

15 3.87~4.1 (m, 2H, C-2), 4.02 (s, 3H, OCH₃)
5.3 (q, 2H, C-3), 5.33 (d, 1H, C-6)
5.82 (d, 1H, C-7), 7.03 (s, 1H, thiazole-H)
7.1~8.2 (m, 4H, phenyl), 8.8 (s, 1H)

20 Example 21

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-methoxyiminoacetamido]-3-[(1-amino-1,4,5,6-tetrahydropyrimidin-
3-ium)methyl]-ceph-3-em-4-carboxylate

25 By following the procedure in Example 19 except that 2.38g(24mmol)
of 1-amino-1,4,5,6-tetrahydropyrimidine was employed in place of
1-aminobenzimidazole, there was obtained 1.68g of the desired compound
(28%).

R_f = 0.29 (in 80% aqueous acetonitrile)

NMR (DMSO-d₆ + 20% DCl, δ)

1.4~1.8 (q, 2H), 3.3~3.9 (m, 6H)

3.98 (s, 3H, OCH₃), 5.21 (q, 2H, C-3)

5 5.3 (d, 1H, C-6), 5.75 (d, 1H, C-7)

7.04 (s, 1H, thiazole-H), 8.5 (s, 1H)

Preparation Example 1

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylic acid

10

A) In 15ml of N,N-dimethylformamide were dissolved 1.09g(2mmol) of (Z)-2-(2-tritylaminothiazol-4-yl)-2-(2-tert-butoxycarbonylmethoxyimino) acetic acid and 0.88g(2mmol) of diphenylmethyl 7 β -amino-3-acetoxymethyl-ceph-3-em-4-carboxylate, and the solution was stirred and cooled to 0°C. 0.28g(2.1mmol) of 1-hydroxybenzotriazole and then 0.43g(2.1mmol) of dicyclohexylcarbodiimide were added thereto. The reaction mixture was stirred at room temperature for 5 hours and left to stand overnight. The reaction mixture was filtered and the filtered solid was washed with diethyl ether. The filtrate and the washing were combined together and 100ml of water added thereto followed by extraction with ethyl acetate. The organic layer was washed with water, 1N hydrochloric acid, sodium bicarbonate solution and then saturated brine, separated, dried over anhydrous sodium sulfate and concentrated under the reduced pressure. The concentrate was subjected to silica gel chromatography(eluent: 2.5% methanol/dichloromethane). The desired fractions were concentrated under the reduced pressure and

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20

25

crystallized from diisopropylether to give 1.35g of diphenylmethyl (6R, 7R)-7-[(Z)-2-(2-tritylaminothiazol-4-yl)-2-(2-tert-butoxycarbonyl-methoxyimino)acetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylate as a desired compound(70%).

- 5 B) In a mixed solvent of anisole(15ml) and trifluoroacetic acid(15ml) was dissolved 1.35g(1.4mmol) of the product prepared in the above(A) at 0°C and the solution was stirred at room temperature for 2 hours. After completion of the reaction, the reaction solution was concentrated under the reduced pressure and the residue was placed in 150ml of
10 n-hexane cooled to -20°C~-30°C. 70ml of diethyl ether was added thereto and the resulting precipitate was filtered to give 0.75g of (6R, 7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylic acid trifluoroacetate. The solid was suspended in 10ml of water, the pH was adjusted to 6.5 with
15 saturated sodium bicarbonate solution and the solution was washed with ethyl acetate. The aqueous layer was adjusted to pH 1.5 and the resulting precipitate was filtered to give 0.48g of (6R, 7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylic acid as a desired compound(68%).

20 R_f = 0.65 (in 80% aqueous acetonitrile)

NMR (DMSO-d₆, δ)

- 2.11 (s, 3H), 3.25~3.82 (q, 2H, C-2)
4.60 (s, 2H), 4.79~4.89 (d, 2H, C-3)
5.19~5.25 (d, 1H, C-6), 5.79~5.85 (dd, 1H, C-7)
25 6.71 (s, 1H, thiazole-H), 7.27 (br, 2H)
9.47 (d, 1H)

Example 22

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-[(1-amino-1,2,3,6-tetrahydropyridinium)methyl]-ceph-3-em-4-carboxylate

5 In 15ml of water was dissolved 3.75g(25mmol) of sodium iodide and the solution was heated to 70~75°C. To this was added 0.59g(6mmol) of 1-amino-1,2,3,6-tetrahydropyridine and 2.5g(5mmol) of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-acetoxymethyl-
10 ceph-3-em-4-carboxylic acid prepared in Preparation Example 1 was slowly added while adjusting the pH to 6.5~7.0. The mixture was stirred at 70~75°C for 2 hours, cooled to room temperature and the pH was adjusted to 1~1.5 with 3N hydrochloric acid. After stirring for
30 min, the resulting precipitate was filtered off and the filtrate was concentrated under the reduced pressure. A small amount of water was
15 added to the concentrate and chromatography over HP-20(eluent: 80% aqueous acetonitrile) was carried out. The fractions containing desired product were concentrated under the reduced pressure and freeze-dried to give 0.46g of the desired compound(17%).

Rf = 0.28 (in 80% aqueous acetonitrile)

20 NMR (DMSO-d₆, δ)

2.1~2.45 (m, 2H), 3.2~4.4 (m, 6H)

4.71 (s, 2H), 4.8~5.2 (m, 2H, C-2)

5.21 (d, 1H, C-6), 5.5~5.87 (m, 3H)

6.72 (s, 1H, thiazole-H), 7.25 (br, 2H)

25 9.45 (d, 1H, -NH)

Example 23

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-carboxymethoxyiminoacetamido]-3-(1-aminopiperidiniummethyl)-
ceph-3-en-4-carboxylate

- 5 By following the procedure in Example 22 except that 0.65ml(6mmol) of 1-aminopiperidine was employed in place of 1-amino-1,2,3,6-tetrahydropyridine, there was obtained 0.53g of the desired compound (20%).

Rf = 0.33 (in 80% aqueous acetonitrile)

- 10 NMR (20% DCl, δ)

1.53~2.22 (m, 6H, piperidine)
3.3~4.5 (m, 6H, C-2, piperidine), 4.7 (s, 2H)
4.88~5.21 (m, 2H, C-3), 5.35 (d, 1H, C-6)
5.8 (d, 1H, C-7), 7.2 (s, 1H, thiazole-H)

15

Example 24

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-carboxymethoxyiminoacetamido]-3-[(2-amino-1,2,3,4-
tetrahydroisoquinolin-2-ium)methyl]-ceph-3-en-4-carboxylate

- 20 By following the procedure in Example 22 except that 0.89g(6mmol) of 2-amino-1,2,3,4-tetrahydroisoquinoline was employed in place of 1-amino-1,2,3,6-tetrahydropyridine, there was obtained 0.55g of the desired compound (19%).

Rf = 0.38 (in 80% aqueous acetonitrile)

- 25 NMR (DMSO-d₆ + 20% DCl, δ)

3.1~3.48 (m, 2H), 3.4~4.4 (m, 6H)
4.6~5.0 (m, 2H, C-3), 5.2 (d, 1H, C-6)

5.75 (d, 1H, C-7), 7.05 (s, 1H, thiazole-H)
7.12~7.82 (m, 4H, phenyl)

Example 25

- 5 Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-carboxymethoxyiminoacetamido]-3-[(1-amino-1-methyl-4-
piperazinium)methyl]-ceph-3-em-4-carboxylate

By following the procedure in Example 22 except that 0.91g(6mmol) of
1-amino-1-methyl-4-piperazinium chloride hydrochloride was employed in
10 place of 1-amino-1,2,3,6-tetrahydropyridine, there was obtained 1.25g of
the desired compound(45%).

Rf = 0.11 (in 80% aqueous acetonitrile)

NMR (DMSO-d₆, δ)

- 3.0~3.8 (m, 5H), 4.65 (s, 2H)
15 5.1 (d, 1H, C-6), 5.65 (dd, 1H, C-7)
6.05 (s, 2H, NH₂), 6.72 (s, 1H, thiazole-H)
7.2 (br, 2H), 9.3 (d, 1H, -NH)

Example 26

- 20 Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-carboxymethoxyiminoacetamido]-3-[(4-amino-1,2,4-triazol-
2-ium)methyl]-ceph-3-em-4-carboxylate

In 8ml of water was dissolved 2.25g(15mmol) of sodium iodide and the
solution was heated to 70~75°C. 0.3g(3.6mmol) of 4-amino-1,2,4-
25 triazole was added and the pH was adjusted to 6.5~7.0. While
maintaining the pH at 6.5~7.0, 1.5g(3mmol) of (6R,7R)-7-[(Z)-2-
(2-aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-acetoxymethyl-

ceph-3-en-4-carboxylic acid prepared in Preparation Example 1 was slowly added. The reaction solution was stirred at 70~75°C for 2 hours, cooled to room temperature and the pH was adjusted to 1~1.5 with 3N hydrochloric acid. The solution was stirred for 30 min and the resulting precipitate was filtered off. The filtrate was concentrated, a small amount of water was added and the resulting was subjected to HP-20 chromatography (eluent: 80% aqueous acetonitrile). The fractions containing the desired product were concentrated under the reduced pressure and freeze-dried to give 0.39g of the desired compound (25%).

R_f = 0.23 (in 80% aqueous acetonitrile)

NMR (DMSO-d₆ + 20% DCl, δ)

3.25~3.7 (m, 2H, C-2), 4.7 (s, 2H)

5.04 (d, 1H, C-6), 5.1~5.3 (q, 2H, C-3)

5.65 (d, 1H, C-7), 7.02 (s, 1H, thiazole-H)

8.75, 9.8 (s,s, 2H, triazole)

Example 27

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-carboxymethoxyiminoacetamidol]-3-[(1-aminoimidazol-3-ium)methyl]-ceph-3-en-4-carboxylate

By following the procedure in Example 26 except that 0.3g(3.6mmol) of 1-aminoimidazole was employed in place of 4-amino-1,2,4-triazole, there was obtained 0.31g of the desired compound(20%).

R_f = 0.29 (in 80% aqueous acetonitrile)

NMR (DMSO-d₆ + 20% DCl, δ)

3.28~3.8 (m, 2H, C-2), 4.70 (s, 2H)

5.05 (q, 2H, C-3), 5.22 (d, 1H, C-6)

5.75 (d, 1H, C-7), 7.0 (s, 1H, thiazole-H)

7.6, 8.2 (s,s, 2H, imidazole), 9.0 (s, 1H, imidazole)

Example 28

5 Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-carboxymethoxyiminoacetamido]-3-[(1-aminopyrazol-2-ium)
methyl]-ceph-3-em-4-carboxylate

By following the procedure in Example 26 except that 0.3g(3.6mmol)
of 1-aminopyrazole was employed in place of 4-amino-1,2,4-triazole,
10 there was obtained 0.29g of the desired compound(18%).

Rf = 0.29 (in 80% aqueous acetonitrile)

NMR (DMSO-d₆ + 20% DCl, δ)

3.3~3.75 (m, 2H, C-2), 4.75 (s, 2H)

5.10 (q, 2H, C-3), 5.25 (d, 1H, C-6)

15 5.7 (d, 1H, C-7), 6.8 (t, 1H, pyrazole)

7.07 (s, 1H, thiazol-H), 7.7, 8.5 (s,s, 2H, pyrazole)

Example 29

20 Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-carboxymethoxyiminoacetamido]-3-[(1-aminoindazol-2-ium)
methyl]-ceph-3-em-4-carboxylate

By following the procedure in Example 26 except that 0.48g(3.6mmol)
of 1-aminoindazole was employed in place of 4-amino-1,2,4-triazole,
there was obtained 0.32g of the desired compound(19%).

25 Rf = 0.30 (in 80% aqueous acetonitrile)

NMR (DMSO-d₆ + 20% DCl, δ)

3.85~4.1 (m, 2H, C-2), 4.76 (s, 2H)

5.31 (q, 1H, C-3), 5.4 (d, 1H, C-6)
5.85 (d, 1H, C-7), 7.1 (s, 1H, thiazole-H)
7.2~8.18 (m, 4H, phenyl), 8.5 (s, 1H, indazole)

5 Example 30

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-carboxymethoxyiminoacetamido]-3-[(1-aminobenzimidazol-3-
ium)methyl]-ceph-3-em-4-carboxylate

By following the procedure in Example 26 except that 0.48g(3.6nmol)
10 of 1-aminobenzimidazole was employed in place of 4-amino-1,2,4-triazole,
there was obtained 0.49g of the desired compound(28%).

Rf = 0.3 (in 80% aqueous acetonitrile)

NMR (DMSO-d₆ + 20% DCl, δ)

3.83~4.0 (m, 2H, C-2), 4.7 (s, 2H)
15 5.06~5.5 (q, 2H, C-3), 5.19 (d, 1H, C-6)
5.79 (d, 1H, C-7), 7.01 (s, 1H, thiazole-H)
7.5~7.9 (m, 4H, phenyl), 9.5 (s, 1H, imidazole)

Example 31

20 Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-carboxymethoxyiminoacetamido]-3-[(1-amino-1,4,5,6-
tetrahydropyrimidin-3-ium)methyl]-ceph-3-em-4-carboxylate

By following the procedure in Example 26 except that 0.36g(3.6nmol)
of 1-amino-1,4,5,6-tetrahydropyrimidine was employed in place of 4-
25 amino-1,2,4-triazole, there was obtained 0.37g of the desired compound
(23%).

Rf = 0.29 (in 80% aqueous acetonitrile)

NMR -(DMSO-d₆ + 20% DCl, δ)

1.5~1.85 (q, 2H), 3.3~3.92 (m, 6H, C-2)

4.69 (s, 2H), 5.2 (q, 2H, C-3)

5.29 (d, 1H, C-6), 5.8 (d, 1H, C-7)

5 7.05 (s, 1H, thiazole-H), 7.5 (s, 1H)

Preparation Example 2

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-(2-carboxyprop-2-oximinino)acetamido]-3-acetoxymethyl-
10 ceph-3-em-4-carboxylic acid

A) A solution of 1.14g(2mmol) of (Z)-2-(2-tritylaminothiazol-4-yl)-2-(2-tert-butoxycarbonylprop-2-oximinino) acetic acid and 0.88g(2mmol) of 7 β -amino-3-acetoxymethyl-ceph-3-em-4-carboxylate in 15ml of N,N-dimethylformamide was stirred, cooled to 0~5°C, and 0.30g(2.2mmol) of
15 N-hydroxybenzotriazole hydrate and then 0.45g(2.2mmol) of N,N-dicyclohexylcarbodiimide were added thereto. The reaction mixture was stirred at room temperature for 6 hours and left to stand overnight. The reaction mixture was filtered and the filtered solid was washed with a small amount of diethyl ether. The filtrate and the washing were
20 combined together, 100ml of water was added followed by extraction with ethyl acetate. The organic layer was washed with water, 1N hydrochloric acid, sodium bicarbonate solution and then saturated brine, separated, dried over anhydrous sodium sulfate and concentrated under the reduced pressure. The concentrate was subjected to silica
25 gel chromatography (eluent: 2% methanol/dichloromethane). The fractions containing the desired product were concentrated under the reduced pressure and crystallized from diisopropyl ether to give 1.49g

of diphenylmethyl (6R,7R)-7-[(Z)-2-(2-tritylaminothiazol-4-yl)-2-(2-tert-butoxycarbonylprop-2-oxyimino)acetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylate as a desired product(75%).

B) In a mixed solvent of anisole(8ml) and trifluoroacetic acid (15ml) was dissolved 1.49g of the product prepared in the above A) at 0°C and the temperature was raised to room temperature. After stirring for 1.5 hours, the reaction solution was concentrated under the reduced pressure and 60ml of diisopropyl ether was added to precipitate 700mg of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-2-oxyimino)acetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylic acid trifluoroacetate, which was filtered. Water(2.6ml) was added to the solid and the pH was adjusted to 7.0 with saturated sodium bicarbonate solution. Purification by HP-20 chromatography (eluent: 70% aqueous acetonitrile) gave 0.55g of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-2-oxyimino)acetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylic acid (70%).

NMR (DMSO-d₆, δ)

1.32 (d, 6H), 2.22 (s, 3H), 3.52 (q, 2H, C-2)

4.87 (q, 2H, C-3), 5.2 (d, 1H, C-6), 5.75 (dd, 1H, C-7)

6.87 (s, 1H, thiazole-H)

Example 32

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-2-oxyimino)acetamido]-3-[(1-amino-1,2,3,6-tetrahydropyridinium)methyl]-ceph-3-em-4-carboxylate

In 15ml of water was dissolved 3.75g(25mmol) of sodium iodide and the solution was heated to 70~75°C. 0.59g(6mmol) of 1-amino-1,2,3,6-tetrahydropyridine was added and then, while adjusting the pH to 6.5~

7.0, 2.64g(5mmol) of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-2-oxyimino)acetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylic acid prepared in Preparation Example 2 was slowly added. The mixture was stirred at 70~75°C for 2 hours, cooled to room temperature and the pH was adjusted to 1~1.5 with 3N hydrochloric acid. The solution was stirred for 30 min and the precipitate was filtered off. The filtrate was concentrated under the reduced pressure, a small amount of water was added and subjected to HP-20 chromatography (80% aqueous acetonitrile). The fractions containing the desired product were concentrated under the reduced pressure and freeze-dried to give 0.51g of the desired compound(18%).

NMR. (DMSO-d₆ + 20% DCl, δ)

1.34 (d, 6H), 2.0~2.4 (m, 2H)
3.1~3.9 (m, 6H, C-2), 4.0~4.3 (m, 1H, C-3)
4.7~5.1 (m, 2H, C-3), 5.2~5.88 (m, 3H, C-7)
6.97 (s, 2H, thiazole-H)

Example 33

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-2-oxyimino)acetamido]-3-(1-aminopiperidinium-methyl)-ceph-3-em-4-carboxylate

By following the procedure in Example 32 except that 0.65ml(6mmol) of 1-aminopiperidine was employed in place of 1-amino-1,2,3,6-tetrahydropyridine, there was obtained 0.53g of the desired compound (19%).

NMR. (DMSO-d₆ + 20% DCl, δ)

1.30 (d, 6H), 1.5~2.3 (m, 6H)

3.2~4.3 (m, 7H), 4.78~5.1 (m, 1H, C-3)

5.2 (d, 1H, C-6), 5.7 (d, 1H, C-7)

7.02 (s, 1H, thiazole-H)

5 Example 34

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-(2-carboxyprop-2-oxylimino)acetamido]-3-[(2-amino-1,2,3,4-
tetrahydroisoquinolin-2-ium)methyl]-ceph-3-en-4-carboxylate

By following the procedure in Example 32 except that 0.89g(6mmol) of
10 2-amino-1,2,3,4-tetrahydroisoquinoline was employed in place of
1-amino-1,2,3,6-tetrahydropyridine, there was obtained 0.52g of the
desired compound(17%).

NMR (DMSO-d₆ + 20% DCl, δ)

1.28 (d, 6H), 3.1~3.51 (m, 2H)

15 3.6~4.3 (m, 7H), 4.5~5.1 (m, 1H, C-3)

5.2 (dd, 1H, C-6), 5.75 (dd, 1H, C-7)

6.95 (s, 1H, thiazole-H), 7.1~7.7 (m, 4H, phenyl)

Example 35

20 Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-(2-carboxyprop-2-oxylimino)acetamido]-3-[(1-amino-1-methyl-
4-piperazinium)methyl]-ceph-3-en-4-carboxylate

By following the procedure in Example 32 except that 0.91g(6mmol) of
1-amino-1-methyl-4-piperazinium chloride hydrochloride was employed in
25 place of 1-amino-1,2,3,6-tetrahydropyridine, there was obtained 0.94g of
the desired compound(32%).

NMR (DMSO-d₆ + 20% DCl, δ)

1.32 (d, 6H), 3.0~3.8 (m, 15H)
4.96 (d, 1H, C-6), 5.51 (d, 1H, C-7)
7.01 (s, 1H, thiazole-H)

5 Example 36

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-(2-carboxyprop-2-oxyimino)acetamido]-3-[(4-amino-1,2,4-
triazol-2-ium)methyl]-ceph-3-em-4-carboxylate

In 8ml of water was dissolved 2.75g(15mmol) of sodium iodide, the
10 solution was heated to 70~75°C and 0.3g(3.6mmol) of 4-amino-1,2,4-
triazole was added. While adjusting the pH to 6.5~7, 1.5g(3mmol) of
(6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-2-oxyimino)
acetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylic acid prepared in
Preparation Example 2 was slowly added. The mixture was stirred at 70.
15 ~75°C for 3 hours, cooled to room temperature and the pH was adjusted
to 1~1.5 with 3N hydrochloric acid. The mixture was stirred for 30
min and the resulting precipitate was filtered off. The filtrate was
concentrated under the reduced pressure, a small amount of water was
added and subjected to HP-20 chromatography (80% aqueous acetonitrile).
20 The fractions containing the desired product were concentrated under the
reduced pressure and freeze-dried to give 0.35g of the desired
compound(20%).

MS(FAB, M+1) = 552

NMR (DMSO-d₆ + 20% DCl, δ)

25 1.30 (d, 6H), 3.3~3.6 (m, 2H, C-2)
5.07 (d, 1H, C-6), 5.0~5.37(q, 2H, C-3)
5.7 (d, 1H, C-7), 7.01 (s, 1H, thiazole-H)

8.7, 9.8 (s,s, 2H, triazole)

Example 37

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-

5 2-(2-carboxyprop-2-oxylimino)acetamido]-3-[(1-aminoimidazol-
3-ium)methyl]-ceph-3-en-4-carboxylate

By following the procedure in Example 36 except that 0.3g(3.6mmol) of 1-aminoimidazole was employed in place of 4-amino-1,2,4-triazole, there was obtained 0.36g of the desired compound(23%).

10 NMR (DMSO-d₆ + 20% DCl, δ)

1.33 (d, 6H), 3.3~3.7 (m, 2H, C-2)

4.9~5.3 (m, 3H, C-6, C-3), 5.7 (d, 1H, C-7)

6.98 (s, 1H, thiazole-H), 7.7, 8.6 (s,s, 2H)

9.1 (t, 1H)

15

Example 38

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-

2-(2-carboxyprop-2-oxylimino)acetamido]-3-[(1-aminopyrazol-
2-ium)methyl]-ceph-3-en-4-carboxylate

20 By following the procedure in Example 36 except that 0.3g(3.6mmol) of 1-aminopyrazole was employed in place of 4-amino-1,2,4-triazole, there was obtained 0.34g of the desired compound(22%).

NMR (DMSO-d₆ + 20% DCl, δ)

1.3 (d, 6H), 3.2~3.7 (m, 2H, C-2)

25 4.9~5.25 (m, 3H, C-3, C-6), 5.65 (d, 1H, C-7)

6.75 (s, 1H), 7.01 (s, 1H, thiazole-H)

7.8, 8.5 (s,s, 2H)

Example 39

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-(2-carboxyprop-2-oxylimino)acetamido]-3-[(1-aminoindazol-
2-ium)methyl]-ceph-3-em-4-carboxylate

- 5 By following the procedure in Example 36 except that 0.48g(3.6mmol)
of 1-aminoindazole was employed in place of 4-amino-1,2,4-triazole,
there was obtained 0.35g of the desired compound(20%).

NMR (DMSO-d₆ + 20% DCl, δ)

- 1.32 (d, 6H), 3.87~4.1 (m, 2H, C-2)
10 5.1~5.4 (m, 3H, C-3, C-6), 5.80 (d, 1H, C-7)
7.03 (s, 1H, thiazole-H), 7.1~8.2 (m, 4H, phenyl)
8.9 (s, 1H)

Example 40

- 15 Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-(2-carboxyprop-2-oxylimino)acetamido]-3-[(1-aminobenzimidzol-
3-ium)methyl]-ceph-3-em-4-carboxylate

- By following the procedure in Example 36 except that 0.48g(3.6mmol)
of 1-aminobenzimidazole was employed in place of 4-amino-1,2,4-triazole,
20 there was obtained 0.38g of the desired compound(22%).

NMR (DMSO-d₆ + 20% DCl, δ)

- 1.29 (d, 6H), 3.2~3.8 (m, 2H, C-2)
5.1~5.4 (m, 3H, C-3, C-6), 5.7 (d, 1H, C-7)
7.03 (s, 1H, thiazole-H), 7.35~8.01 (m, 4H, phenyl)
25 9.7 (s, 1H; imidazole-H)

Example 41

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-(2-carboxyprop-2-oxyimino)acetamido]-3-[(1-amino-1,4,5,6-
tetrahydropyrimidin-3-ium)methyl]-ceph-3-em-4-carboxylate

- 5 By following the procedure in Example 36 except that 0.36g(3.6mmol) of 1-amino-1,4,5,6-tetrahydropyrimidine was employed in place of 4-amino-1,2,4-triazole, there was obtained 0.31g of the desired compound(19%).

NMR (DMSO-d₆ + 20% DCl, δ)

- 10 1.32 (d, 6H), 1.4~1.8 (q, 2H)
3.3~3.9 (m, 6H, C-2), 5.15~5.4 (m, 3H, C-3, C-6)
5.76 (d, 1H, C-7), 7.01 (s, 1H, thiazole-H)
8.5 (s, 1H)

15 Preparation Example 3

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-(2-carboxyprop-2-oxyimino)acetamidol]-3-acetoxymethyl-
ceph-3-em-4-carboxylic acid

- A) In 15ml of N,N-dimethylformamide was dissolved 1.22g(3mmol) of
20 (Z)-2-[(2-chloroacetamidothiazol-4-yl)-2-(2-tert-butoxycarbonylprop-2-
oxyimino)acetic acid, 0.66g(3.21mmol) of N,N-dicyclohexylcarbodiimide
was added thereto and the mixture was stirred at room temperature for 2
hours. 1.41g(3.21mmol) of diphenylmethyl 7 β -amino-3-acetoxymethyl-
ceph-3-em-4-carboxylate was added thereto at 0~5°C and the mixture was
25 stirred at the same temperature for 4.5 hours.

After completion of the reaction, the insoluble was filtered off,
200ml of dichloromethane was added to the filtrate and this was washed

with diluted hydrochloric acid and then with water. The organic layer was dried over anhydrous magnesium sulfate and concentrated under the reduced pressure. The residue was purified by silica gel column chromatography using 6% methanol/dichloromethane as an eluent to give 5 1.86g of diphenylmethyl (6R,7R)-7-[(Z)-2-(2-chloroacetamidothiazol-4-yl)-2-(2-tert-butoxycarbonylprop-2-oxyimino)acetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylate in pale yellow powder form(70%).

B) In 15ml of anisole was dissolved the product obtained in the above A), the solution was cooled to 0~5°C and 15ml of trifluoroacetic acid 10 was added thereto. The reaction mixture was stirred at the same temperature for 2 hours.

After completion of the reaction, the reaction solution was concentrated under the reduced pressure to remove trifluoroacetic acid. The residue was cooled to -20~-10°C, 200ml of diisopropyl ether was 15 added and the mixture was stirred at the same temperature for 1 hour. The resulting precipitate was filtered, washed thoroughly with diisopropyl ether and dried to give 1.37g of (6R,7R)-7-[(Z)-2-(2-chloroacetamidothiazol-4-yl)-2-(2-carboxyprop-2-oxyimino)acetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylic acid trifluoroacetate (85%).

20 C) The product obtained in the above B) was suspended in 70ml of water and the pH was adjusted to 6.5~7.0 with saturated sodium bicarbonate solution. 0.26g(2mmol) of sodium N-methyl-dithiocarbamate was added thereto and the mixture was stirred at room temperature for 5 hours.

25 After completion of the reaction, the reaction mixture was washed with ethyl acetate and the aqueous layer containing the desired product was concentrated under the reduced pressure. The concentrate was

purified by HP-20 column chromatography. The fractions containing the desired product were concentrated under the reduced pressure and freeze-dried to give 0.73g of (6R,7R)-[(Z)-2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-2-oxyimino)acetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylic acid(72%).

Rf = 0.5 (in 80% aqueous acetonitrile)

The NMR spectra of the desired compound were the same as those of the compound obtained in Preparation Example 2.

10 Example 42

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-2-oxyimino)acetamido]-3-[(4-aminomorpholin-4-ium)methyl]-ceph-3-em-4-carboxylate

In a mixed solvent of acetonitrile(10ml) and water(10ml) was dissolved 6.69g(50mmol) of lithium iodide, 1.02g(10mmol) of 4-amino morpholine was added thereto and the mixture was heated to 65~68°C. Water(4ml) containing 2.64g(5mmol) of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-2-oxyimino)acetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylic acid prepared in Preparation Example 3 and 0.1g of sodium hydroxide was added thereto and the reaction mixture was stirred at 70~72°C for 1.5 hours while adjusting the pH to 6.5~7.0.

After completion of the reaction, the reaction solution was cooled to room temperature and the pH was adjusted to 1.5 with 3N hydrochloric acid. The insoluble was filtered off and the filtrate was concentrated under the reduced pressure followed by purification by column chromatography over aluminium oxide (eluent: 80% aqueous acetonitrile). The fractions were concentrated under the reduced pressure, dissolved in

a small amount of water and purified by HP-20 column chromatography. The fractions containing the desired product were concentrated under the reduced pressure and freeze-dried to give 0.47g of the desired compound (16%).

5 NMR (DMSO-d₆ + 20% DCl, δ)

1.3 (d, 6H), 3.35~4.55 (m, 11H)

4.95~5.36 (q, 1H, C-3), 5.34 (d, 1H, C-6)

5.8 (d, 1H, C-7), 7.02 (s, 1H, thiazole-H)

10 Example 43

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-(2-carboxyprop-2-oxylimino)acetamido]-3-(1-
aminopyrrolidiniummethyl)-ceph-3-em-4-carboxylate

By following the procedure in Example 42 except that 1.23g(10mmol)

15 of 1-aminopyrrolidine was employed in place of 4-aminomorpholine, there was obtained 0.51g of the desired compound(18%).

NMR (DMSO-d₆ + 20% DCl, δ)

1.34 (d, 6H), 1.75~2.25 (m, 4H)

2.92~3.75 (m, 6H), 3.8~4.2 (m, 1H, C-3)

20 4.4~5.0 (m, 1H, C-3), 5.2 (d, 1H, C-6)

5.7 (d, 1H, C-7), 7.02 (s, 1H, thiazole-H)

Example 44

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
25 2-(2-carboxyprop-2-oxylimino)acetamido]-3-[(1-amino-3-
pyrrolin-1-ium)methyl]-ceph-3-em-4-carboxylate

By following the procedure in Example 42 except that 0.84g(10mmol)

of 1-amino-3-pyrroline was employed in place of 4-aminomorpholine, there was obtained 0.39g of the desired compound(14%).

NMR (DMSO-d₆ + 20% DCl, δ)

- 1.30 (d, 6H), 3.6~4.1 (m, 3H, C-2, C-3)
5 4.65 (s, 4H), 4.57~5.1 (m, 1H, C-3)
5.2 (d, 1H, C-6), 5.65 (d, 1H, C-7)
7.03 (s, 1H, thiazole-H)

Example 45

- 10 Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-(2-carboxyprop-2-oxyimino)acetamidol-3-(1-
aminoindoliniummethyl)-ceph-3-en-4-carboxylate

- By following the procedure in Example 42 except that 1.34g(10mmol)
of 1-aminoindoline was employed in place of 4-aminomorpholine, there was
15 obtained 0.48g of the desired compound(16%).

NMR (DMSO-d₆ + 20% DCl, δ)

- 1.32 (d, 6H), 2.8~3.2 (m, 2H)
3.4~4.5 (m, 5H), 4.6~5.2 (m, 2H, C-3, C-6)
5.65 (d, 1H, C-7), 7.01 (s, 1H, thiazole-H)
20 7.05~7.8 (m, 4H, phenyl)

Example 46

- Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-(2-carboxyprop-2-oxyimino)acetamidol-3-(1-
25 aminopyrroliniummethyl)-ceph-3-en-4-carboxylate

- By following the procedure in Example 42 except that 0.82g(10mmol)
of 1-aminopyrrole was employed in place of 4-aminomorpholine, there was

obtained 0.45g of the desired compound(16%).

NMR (DMSO-d₆ + 20% DCl, δ)

1.28 (d, 6H), 3.64 (m, 3H, C-2, C-3)

4.6~5.2 (m, 2H, C-3, C-6), 5.6 (d, 1H, C-7)

5 6.2 (t, 2H), 6.6 (t, 2H)

7.03 (s, 1H, thiazole-H)

Example 47

10 Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-(2-carboxyprop-2-oxyimino)acetamido]-3-(1-
aminoindoliummethyl)-ceph-3-em-4-carboxylate

By following the procedure in Example 42 except that 1.32g(10mmol)
of 1-aminoindole was employed in place of 4-aminomorpholine, there was
obtained 0.49g of the desired compound(16%).

15 NMR (DMSO-d₆ + 20% DCl, δ)

1.29 (d, 6H), 3.5~4.0 (m, 3H, C-2, C-3)

4.6~5.2 (m, 2H, C-3, C-6), 5.65 (d, 1H, C-7)

6.5 (d, 1H), 7.02 (s, 1H, thiazole-H)

7.05~7.9 (m, 5H, phenyl)

20

Example 48

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-(2-carboxyprop-2-oxyimino)acetamido]-3-[(1-amino-4-
hydroxypiperidinium)methyl]-ceph-3-em-4-carboxylate

25 By following the procedure in Example 42 except that 1.16g(10mmol)
of 1-amino-4-hydroxypiperidine was employed in place of 4-
aminomorpholine, there was obtained 0.51g of the desired compound(17%).

Rf = 0.14 (in 80% aqueous acetonitrile)

NMR (20% DCI, δ)

1.18~2.0 (m, 4H), 1.30 (d, 6H)

3.2~4.3 (m, 7H), 4.86~5.2 (m, 2H, C-3)

5 5.35 (d, 1H, C-6), 5.93 (d, 1H, C-7)

7.21 (s, 1H, thiazole-H)

Example 49

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
10 2-(2-carboxyprop-2-oxyimino)acetamido]-3-[(1-amino-1,2,3-
triazol-3-ium)methyl]-ceph-3-em-4-carboxylate

In a mixed solvent of acetonitrile(10ml) and water(15ml) was
dissolved 5.35g(40mmol) of lithium iodide, 0.673g(8mmol) of 1-amino-
1,2,3-triazole was added thereto and the mixture was heated to 65~68°C.
15 2.11g(4mmol) of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-(2-carboxy-
prop-2-oxyimino)acetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylic acid
prepared in Preparation Example 3 was added and the mixture was stirred
at 70~72°C for 2 hours while adjusting the pH to 6.5~7.0.

After completion of the reaction, the reaction solution was cooled
20 to room temperature and the pH was adjusted to 1~1.5 with 3N
hydrochloric acid. The insoluble was filtered off and the filtrate was
concentrated under the reduced pressure followed by column
chromatography over aluminium oxide using 80% aqueous acetonitrile
solution as an eluent. The fractions were concentrated under the
25 reduced pressure, dissolved in a small amount of water and purified by
HP-20 column chromatography. The fractions containing the desired
product were concentrated under the reduced pressure and freeze-dried to

give 0.68g of the desired compound(31%).

NMR (DMSO-d₆ + 20% DCl, δ)

1.3 (d, 6H), 3.4~3.7 (m, 2H, C-2)

5.05~5.18 (m, 3H, C-3, C-6), 5.67 (d, 1H, C-7)

5 7.02 (s, 1H, thiazole-H), 7.8, 8.7 (s,s, 2H, triazole-H)

Example 50

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-

2-(2-carboxyprop-2-oxyimino)acetamido]-3-[(1-aminobenzotriazol-

10 3-ium)methyl]-ceph-3-em-4-carboxylate

By following the procedure in Example 49 except that 1.07g(8mmol) of 1-aminobenzotriazole was employed in place of 1-amino-1,2,3-triazole, there was obtained 0.53g of the desired compound(22%).

MS(FAB, M+1) = 602

15 NMR (DMSO-d₆ + 20% DCl, δ)

1.31 (d, 6H), 3.86~4.1 (m, 2H, C-2)

5.05~5.55 (m, 3H, C-3, C-6), 5.87 (d, 1H, C-7)

7.02 (s, 1H), 7.7~8.15 (m, 4H, phenyl)

20 Example 51

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-

2-(2-carboxyprop-2-oxyimino)acetamido]-3-[(1-amino-1,2,4-

triazol-4-ium)methyl]-ceph-3-en-4-carboxylate

By following the procedure in Example 49 except that 0.67g(8mmol) of 25 1-amino-1,2,4-triazole was employed in place of 1-amino-1,2,3-triazole, there was obtained 0.5g of the desired compound(23%).

NMR (DMSO-d₆ + 20% DCl, δ)

1.28 (d, 6H), 3.29~3.74 (m, 2H, C-2)

5.05~5.25 (m, 3H, C-3, C-6), 5.7 (d, 1H, C-7)

6.94 (s, 1H, thiazole-H), 8.74, 9.68 (s,s, 2H, triazole)

5 Example 52

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-(2-carboxyprop-2-oxylimino)acetamido]-3-[(1-aminotetrazol-4-
ium)methyl]-ceph-3-em-4-carboxylate

By following the procedure in Example 49 except that 0.69g (8mmol)
10 of 1-aminotetrazole was employed in place of 1-amino-1,2,3-triazole,
there was obtained 0.48g of the desired compound (22%).

NMR(DMSO-d₆ + 20% DCl, δ)

1.29 (d, 3H), 3.3~3.76 (m, 2H, C-2)

5.05~5.2 (m, 3H, C-3, C-6), 5.7 (d, 1H, C-7)

15 6.99 (s, 1H, thiazole-H), 9.52 (s, 1H, tetrazole-H)

Preparation Example 4

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-carboxymethoxyiminoacetamido]-3-acetoxymethyl-
20 ceph-3-em-4-carboxylic acid

A) In 15ml of N,N-dimethylformamide was dissolved 1.13g(3mmol) of
(Z)-2-[(2-chloroacetamidothiazol-4-yl)-2-tert-butoxycarbonylmethoxy-
imino]acetic acid, and 0.43g(3.18mmol) of N-hydroxybenzotriazole and
0.66g(3.21mmol) of N,N-dicyclohexylcarbodiimide were added thereto. The
25 reaction mixture was stirred at room temperature for 2 hours.

1.41g(3.21mmol) of diphenylmethyl 7 β -amino-3-acetoxymethyl-ceph-3-
em-4-carboxylate was added at 0~5°C and the mixture was stirred at the

same temperature for 5 hours. After completion of the reaction, the procedure in Preparation Example 3-A) was repeated to give 1.67g of diphenylmethyl(6R,7R)-7-[(Z)-2-(2-chloroacetamidothiazol-4-yl)-2-tert-butoxycarbonylmethoxyiminoacetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylate(65%).

B) The product obtained in the above A) was dissolved in 120ml of anisole and the mixture was cooled to 0~5°C. 12ml of trifluoroacetic acid was added and the reaction mixture was stirred at the same temperature for 2 hours. After completion of the reaction, the procedure in Preparation Example 3-B) was repeated to give 1.2g of (6R,7R)-7-[(Z)-2-(2-chloroacetamidothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylic acid trifluoroacetate(83%).

C) The product obtained in the above B) was suspended in 65ml of water and the pH was adjusted to 6.5~7.0 with saturated sodium bicarbonate solution. 0.34g(2.6mmol) of sodium N-methyl-dithiocarbamate was added and the reaction mixture was stirred at room temperature for 4~5 hours. After completion of the reaction, the procedure in Preparation Example 3-C) was repeated to give 582mg of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylic acid (67%).

Rf = 0.65 (in 80% aqueous acetonitrile)

NMR (DMSO-d₆, δ)

2.11 (s, 3H), 3.25~3.82 (q, 2H, C-2)

4.6 (s, 2H), 4.79~4.89 (d, 2H)

25 5.19~5.25 (d, 1H, C-6), 5.79~5.85 (dd, 1H, C-7)

6.71 (s, 1H, thiazole-H), 7.27 (br, 2H, NH₂)

9.5 (d, 1H, -NH)

Example 53

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-carboxymethoxyiminoacetamido]-3-[(4-aminomorpholin-
4-ium)methyl]-ceph-3-em-4-carboxylate

- 5 In a mixed solvent of acetonitrile(9ml) and water(10ml) was dissolved 6.69g(50mmol) of lithium iodide, the solution was heated to 65~68°C and 1.02g(10mmol) of 4-aminomorpholine was added thereto. Water (3ml) containing 2.5g(5mmol) of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-acetoxymethyl-ceph-3-em-4-
- 10 carboxylic acid and 0.1g of sodium hydroxide was added and the reaction mixture was stirred at 70~73°C for 2 hours while the pH was adjusted to 6.5~7.0.

- After completion of the reaction, the reaction solution was cooled to room temperature and the pH was adjusted to 1.5 with 3N hydrochloric
- 15 acid. The insoluble was filtered off and the filtrate was concentrated under the reduced pressure followed by aluminium oxide column chromatography using 80% aqueous acetonitrile as an eluent. The fractions were concentrated under the reduced pressure, dissolved in a small amount of water and purified by HP-20 column chromatography. The
- 20 fractions containing the desired product were concentrated under the reduced pressure and freeze-dried to give 0.79g of the desired compound(29%).

Rf = 0.34 (in 80% aqueous acetonitrile)

NMR (20% DCl, δ)

- 25 3.4~4.6 (m, 11H, morpholine, C-2, C-3), 4.7 (s, 2H)
5.0~5.35 (q, 1H, C-3), 5.33 (d, 1H, C-6)
5.8 (d, 1H, C-7), 7.18 (s, 1H, thiazole-H)

Example 54

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-carboxymethoxyiminoacetamido]-3-(1-aminopyrrolidiniummethyl)-
ceph-3-en-4-carboxylate

- 5 By following the procedure in Example 53 except that 1.23g(10mmol)
of 1-aminopyrrolidine was employed in place of 4-aminomorpholine, there
was obtained 0.49g of the desired compound(19%).

Rf = 0.3 (in 80% aqueous acetonitrile)

NMR (20% DCI, δ)

- 10 1.75~2.3 (m, 4H, pyrrolidine), 2.91~3.8 (m, 6H, C-2, pyrrolidine)
3.9~4.4 (m, 1H, C-3), 4.65 (s, 2H)
4.5~4.95 (m, 1H, C-3), 5.15 (dd, 1H, C-6)
5.7 (dd, 1H, C-7), 7.12 (s, 1H, thiazole-H)

15 Example 55

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-carboxymethoxyiminoacetamido]-3-[(1-amino-3-pyrroline-1-
ium)methyl]-ceph-3-en-4-carboxylate

- 20 By following the procedure in Example 53 except that 0.84g(10mmol)
of 1-amino-3-pyrroline was employed in place of 4-aminomorpholine, there
was obtained 0.47g of the desired compound(18%).

Rf = 0.3 (in 80% aqueous acetonitrile)

NMR (DMSO-d₆ + 20% DCI, δ)

- 25 3.5~4.1 (m, 3H, C-2, C-3), 4.6 (s, 4H, pyrroline)
4.56~5.1 (m, 1H, C-3), 4.7 (s, 2H)
5.16 (d, 1H, C-6), 5.7 (d, 1H, C-7)
5.92 (s, 2H, pyrroline), 7.04 (s, 1H, thiazole-H)

Example 56

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-carboxymethoxyiminoacetamido]-3-(1-aminoindoliniummethyl)-
-ceph-3-em-4-carboxylate

5 By following the procedure in Example 53 except that 1.34g(10mmol)
of 1-aminoindoline was employed in place of 4-aminomorpholine, there
was obtained 0.5g of the desired compound(17%).

Rf = 0.37 (in 80% aqueous acetonitrile)

NMR (DMSO-d₆ + 20% DCl, δ)

10 2.8~3.2 (m, 2H, indole)
3.4~4.4 (m, 5H, indole, C-2, C-3), 4.65 (s, 2H)
4.7~5.1 (m, 1H, C-3), 5.12 (d, 1H, C-6)
5.7 (d, 1H, C-7), 7.02 (s, 1H, thiazole-H)
7.04~7.8 (m, 4H, phenyl)

15

Example 57

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-carboxymethoxyiminoacetamido]-3-(1-aminopyrroliniummethyl)-
-ceph-3-em-4-carboxylate

20 By following the procedure in Example 53 except that 0.82g(10mmol)
of 1-aminopyrrole was employed in place of 4-aminomorpholine, there was
obtained 0.43g of the desired compound(16%).

Rf = 0.28 (in 80% aqueous acetonitrile)

NMR (DMSO-d₆ + 20% DCl, δ)

25 3.6~4.0 (m, 3H, C-2, C-3), 4.65 (s, 2H)
4.6~5.0 (m, 1H, C-3), 5.2 (d, 1H, C-6)
5.65 (d, 1H, C-7), 6.12 (t, 2H, pyrrole)

6.5 (t, 2H, pyrrole), 7.03 (s, 1H, thiazole-H)

Example 58

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)]-

5 2-carboxymethoxyiminoacetamidol-3-(1-aminoindoliummethyl)-
-ceph-3-em-4-carboxylate

By following the procedure in Example 53 except that 1.32g(10mmol) of 1-aminoindole was employed in place of 4-aminomorpholine, there was obtained 0.41g of the desired compound(14%).

10 R_f = 0.35 (in 80% aqueous acetonitrile)

NMR (DMSO-d₆ + 20% DCl, δ)

3.47~4.0 (m, 3H, C-2, C-3), 4.62~5.0 (m, 1H, C-3)

4.7 (s, 2H), 5.2 (d, 1H, C-6)

5.55 (d, 1H, C-7), 6.47 (d, 1H, indole)

15 7.01 (s, 1H, thiazole-H), 7.03~8.0 (m, 5H, phenyl)

Example 59

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)]-

20 2-carboxymethoxyiminoacetamidol-3-[(1-amino-4-
hydroxypiperidinium)methyl]-ceph-3-em-4-carboxylate

By following the procedure in Example 53 except that 1.16g(10mmol) of 1-amino-4-hydroxypiperidine was employed in place of 4-aminomorpholine, there was obtained 0.56g of the desired compound(20%).

R_f = 0.14 (in 80% aqueous acetonitrile)

25 NMR (20% DCl, δ)

1.2~2.0 (m, 4H), 3.22~4.4 (m, 7H)

4.70 (s, 2H), 4.85~5.21 (m, 2H, C-3)

5.35 (d, 1H, C-6), 5.95 (d, 1H, C-7)

7.22 (s, 1H, thiazole-H)

Example 60

- 5 Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-carboxymethoxyiminoacetanido]-3-[(1-amino-1,2,3-
triazol-3-ium)methyl]-ceph-3-en-4-carboxylate

10 In a mixed solvent of acetonitrile (9ml) and water(15ml) was
dissolved 5.35g(40mmol) of lithium iodide, 0.673g(8mmol) of 1-amino-
1,2,3-triazole was added thereto and the mixture was heated to 68°C.
2g(4mmol) of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-carboxymethoxy-
iminoacetanido]-3-acetoxymethyl-ceph-3-en-4-carboxylic acid prepared in
Preparation Example 4 was added and the mixture was stirred at 70~72°C
for 1.5 hours while adjusting the pH to 6.5~7.0.

15 After completion of the reaction, the reaction solution was cooled
to room temperature and the pH was adjusted to 1.5 with 3N hydrochloric
acid. The insoluble was filtered off and the filtrate was concentrated
under the reduced pressure followed by aluminium oxide column
chromatography using 80% aqueous acetonitrile as an eluent. The
20 fractions were concentrated under the reduced pressure, dissolved in a
small amount of water and purified by HP-20 column chromatography. The
fractions containing the desired product were concentrated under the
reduced pressure and freeze-dried to give 0.48g of the desired
compound(23%).

25 R_f = 0.25 (in 80% aqueous acetonitrile)

NMR (DMSO-d₆ + 20% DCl, δ)

3.4~3.72 (m, 2H, C-2), 4.75 (s, 2H), 5.13 (q, 2H, C-3)

5.16 (d, 1H, C-6), 5.7 (d, 1H, C-7)

7.02 (s, 1H, thiazole-H), 7.8, 8.8 (s,s, 2H, triazole)

Example 61

- 5 Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-carboxymethoxyiminoacetamido]-3-[(1-aminobenzotriazol-
3-ium)methyl]-ceph-3-em-4-carboxylate

By following the procedure in Example 60 except that 1.07g(8mmol) of
1-aminobenzotriazole was employed in place of 1-amino-1,2,3-triazole,
10 there was obtained 0.51g of the desired compound(22%).

Rf = 0.3 (in 80% aqueous acetonitrile)

MS(FAB, M+1) = 574

NMR (DMSO-d₆ + 20% DCl, δ)

3.82~4.1 (m, 2H, C-2), 4.72 (s, 2H)

15 5.1~5.45 (q, 2H, C-3), 5.35 (d, 1H, C-6)

5.85 (d, 1H, C-7), 7.02 (s, 1H, thiazole-H)

7.5~8.2 (m, 4H, phenyl)

Example 62

- 20 Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-carboxymethoxyiminoacetamido]-3-[(1-amino-1,2,4-
triazol-4-ium)methyl]-ceph-3-em-4-carboxylate

By following the procedure in Example 60 except that 0.67g(8mmol) of
1-amino-1,2,4-triazole was employed in place of 1-amino-1,2,3-triazole,
25 there was obtained 0.53g of the desired compound(25%).

Rf = 0.3 (in 80% aqueous acetonitrile)

NMR (DMSO-d₆ + 20% DCl, δ)

3.4~3.8 (m, 2H, C-2), 4.65 (s, 2H)
5.12 (q, 2H, C-3), 5.2 (d, 1H, C-6)
5.6 (d, 1H, C-7), 6.99 (s, 1H, thiazole-H)
8.75, 9.68 (s,s, 2H, triazole)

5

Example 63

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-carboxymethoxyiminoacetamido]-3-[(1-aminotetrazol-4-
ium)methyl]-ceph-3-em-4-carboxylate

10 By following the procedure in Example 60 except that 0.69g(8mmol) of
1-aminotetrazole was employed in place of 1-amino-1,2,3-triazole, there
was obtained 0.43g of the desired compound(19%).

Rf = 0.24 (in 80% aqueous acetonitrile)

NMR (DMSO-d₆ + 20% DCl, δ)

15 3.23~3.8 (m, 2H, C-2), 4.68 (s, 2H)
5.1 (q, 2H, C-3), 5.25 (d, 1H, C-6)
5.7 (d, 1H, C-7), 7.05 (s, 1H, thiazole-H)
9.6 (s, 1H, tetrazole-H)

20 Preparation Example 5

Synthesis of (6R,7R)-7-[(Z)-2-(2-tritylaminothiazol-
4-yl)-2-methoxyiminoacetamido]-3-chloromethyl-ceph-
3-em-4-carboxylate

To 10ml of dichloromethane were added 0.45g(1mmol) of diphenylmethyl
25 7β-amino-3-chloromethyl-ceph-3-em-4-carboxylate hydrochloride and 0.53g
(1.2mmol) of (Z)-2-(2-tritylaminothiazol-4-yl)-2-methoxyiminoacetic
acid. 0.4ml(5mmol) of pyridine and 0.11ml(1.2mmol) of phosphorus

oxychloride were slowly added under ice-cooling and the mixture was stirred for 15min. 50ml of chloroform was added, and the mixture was washed with water and dried over anhydrous sodium sulfate.

The solution was concentrated under the reduced pressure and subjected to silica gel chromatography (2% methanol/dichloromethane). The fractions containing the desired product were concentrated under the reduced pressure and crystallized from diisopropyl ether to give 0.6g of the desired compound (72%).

NMR (CDCl₃, δ)

10 3.55 (bs, 2H), 4.05 (s, 3H), 4.30 (bs, 2H)
5.05 (d, 1H), 5.90 (dd, 1H), 6.75 (s, 1H)
6.95 (s, 1H), 7.1~7.8 (m, 26H)

Preparation Example 6

15 Synthesis of diphenylmethyl (6R,7R)-7-[(Z)-2-(2-tritylaminothiazol-4-yl)-2-methoxyiminoacetamido]-3-chloromethyl-ceph-3-em-4-carboxylate

To 25ml of N,N-dimethylformamide were added 1.3g(3mmol) of (Z)-2-(2-tritylaminothiazol-4-yl)-2-methoxyiminoacetic acid and 1.35(3mmol) of 20 diphenylmethyl 7 β -amino-3-chloromethyl-ceph-3-em-4-carboxylate hydrochloride. The mixture was cooled to 0°C, and 0.53g(3.9mmol) of N-hydroxybenzotriazole hydrate and then 0.80g (3.9mmol) of N,N-dicyclohexylcarbodiimide were added thereto.

The reaction mixture was stirred for 5 hours and left to stand 25 overnight. The reaction mixture was filtered and the filtered solid was washed with a small amount of diethyl ether. The filtrate and the washing were combined together and 125ml of water was added thereto.

The reaction mixture was extracted with ethyl acetate and washed with sodium bicarbonate solution and then saturated brine. The organic layer was dried over anhydrous sodium sulfate, concentrated under the reduced pressure and subjected to silica gel chromatography (2% methanol/ dichloromethane). The fractions containing the desired product were concentrated under the reduced pressure and crystallized from diisopropyl ether to give 1.92g of the desired compound(76%).

NMR (CDCl₃, δ)

3.55 (bs, 2H), 4.05 (s, 3H), 4.30 (bs, 2H)
5.05 (d, 1H), 5.90 (dd, 1H), 6.75 (s, 1H)
6.95 (s, 1H), 7.1~7.8 (m, 26H)

Example 64

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-aminopiperidinumethyl)-ceph-3-en-4-carboxylate

A) In 5ml of N,N-dimethylformamide were dissolved 2.52g(3.0mmol) of diphenylmethyl (6R,7R)-7-[(Z)-2-(2-tritylaminothiazol-4-yl)-2-methoxyiminoacetamido]-3-chloromethyl-ceph-3-en-4-carboxylate prepared in Preparation Example 5 or 6 and 0.67g(0.45mmol) of sodium iodide and 0.39ml (3.6mmol) of 1-aminopiperidine was added thereto. The mixture was stirred at room temperature for 3 hours. To the reaction solution was added 15ml of water and the mixture was extracted with dichloromethane. The organic layer was washed with water, dried over anhydrous magnesium sulfate, concentrated under the reduced pressure and subjected to silica gel chromatography (4% methanol/dichloromethane). The fractions containing the desired product were concentrated under the

reduced pressure to give 1.86g of diphenylmethyl (6R,7R)-7-[(Z)-2-(2-tritylaminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-aminopiperidinium methyl)-ceph-3-em-4-carboxylate iodide(60%).

5 B) To 1.7ml of anisole was added 0.6g(0.58mmol) of the product obtained in the above A), 5.6ml of trifluoroacetic acid was slowly added under ice-cooling and the mixture was stirred for 1 hour. Diisopropyl ether was added, and the resulting precipitate was filtered and dried. A small amount of water was added to the solid, and the pH was adjusted to 5~8 with saturated sodium bicarbonate solution. HP-20 column
10 chromatography was carried out by using 80% aqueous acetonitrile solution as an eluent. The fractions containing the desired product were concentrated under the reduced pressure and freeze-dried to give 0.24g of the desired compound (82%).

The NMR spectra of the desired compound were the same as those of
15 the compound prepared in Example 3.

Example 65

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-methoxyiminoacetamido]-3-[(4-aminomorpholin-4-ium)
20 methyl]-ceph-3-em-4-carboxylate

By following the procedure in Example 64 except that 0.35g(3.6mmol) of 4-aminomorpholine was employed in place of 1-aminopiperidine, there was obtained 0.63g of the desired compound (43%).

The NMR spectra of the desired compound were the same as those of
25 the compound prepared in Example 2.

Example 66

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-methoxyiminoacetamido]-3-(1-aminopyrrolidiniummethyl)-
ceph-3-em-4-carboxylate

- 5 By following the procedure in Example 64 except that 0.44g(3.6mmol)
of 1-aminopyrrolidine was employed in place of 1-aminopiperidine, there
was obtained 0.65g of the desired compound (45%).

The NMR spectra of the desired compound were the same as those of
the compound prepared in Example 1.

10 Example 67

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-methoxyiminoacetamido]-3-[(1-amino-1,2,3,6-tetrahydro-
pyridinium)methyl]-ceph-3-em-4-carboxylate

- By following the procedure in Example 64 except that 0.53g(3.6mmol)
15 of 1-amino-1,2,3,6-tetrahydropyridine was employed in place of 1-
aminopiperidine, there was obtained 0.54g of the desired compound (36%).

The NMR spectra of the desired compound were the same as those of
the compound prepared in Example 8.

20 Example 68

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-methoxyiminoacetamido]-3-[(1-amino-4-hydroxypipe-
ridinium)methyl]-ceph-3-em-4-carboxylate

- By following the procedure in Example 64 except that 0.42g(3.6mmol)
25 of 1-amino-4-hydroxypiperidine was employed in place of 1-amino-
piperidine, there was obtained 0.65g of the desired compound (42%).

The NMR spectra of the desired compound were the same as those of

the compound prepared in Example 4.

Example 69

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
2-methoxyiminoacetamido]-3-[(2-amino-1,2,3,4-tetrahydro-
5 isoquinolin-2-ium)methyl]-ceph-3-em-4-carboxylate

By following the procedure in Example 64 except that 0.53g(3.6mmol)
of 2-amino-1,2,3,4-tetrahydroisoquinoline was employed in place of
1-aminopiperidine, there was obtained 0.78g of the desired compound
10 (48%).

The NMR spectra of the desired compound were the same as those of
the compound prepared in Example 5.

Example 70

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-
15 2-methoxyiminoacetamido]-3-[(1-amino-1-methyl-4-
piperazinium)methyl]-ceph-3-em-4-carboxylate

By following the procedure in Example 64 except that 0.55g(3.6mmol)
of 1-amino-1-methyl-4-piperazinium was employed in place of 1-
20 aminopiperidine, there was obtained 1.14g of the desired compound (75%).

The NMR spectra of the desired compound were the same as those of
the compound prepared in Example 11.

Example 71

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-
25 methoxyiminoacetamido]-3-[(4-amino-1,2,4-triazol-2-ium)
methyl]-ceph-3-em-4-carboxylate

A) In 5ml of N,N-dimethylformamide were dissolved 2.52g(3.0mmol) of diphenylmethyl (6R,7R)-7-[(Z)-2-(2-tritylaminothiazol-4-yl)-2-methoxyiminoacetamido]-3-chloromethyl-ceph-3-em-4-carboxylate prepared in Preparation Example 5 or 6 and 1.35g(9.0mmol) of sodium iodide and 0.34g (4.0mmol) of 4-amino-1,2,4-triazole was added thereto. The reaction mixture was stirred at 45~50°C for 3 hours and cooled to room temperature. 15ml of water was added, the reaction mixture was extracted with dichloromethane and the organic layer was washed with water. The dichloromethane layer was dried over anhydrous magnesium sulfate, concentrated under the reduced pressure and subjected to silica gel chromatography (5% methanol/dichloromethane). The fractions containing the desired product were concentrated under the reduced pressure to give 1.71g of diphenylmethyl (6R,7R)-7-[(Z)-2-(2-tritylaminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(4-amino-1,2,4-triazol-2-yl)methyl]-ceph-3-em-4-carboxylate iodide(56%).

B) To 1.6ml of anisole was added 0.56g(0.55mmol) of the compound prepared in the above A), 5.5ml of trifluoroacetic acid was slowly added under ice-cooling and the mixture was stirred for 1 hour. Diisopropyl ether was added, and the resulting precipitate was filtered and dried. A small amount of water was added, the pH was adjusted to 4.5~5 with saturated sodium bicarbonate solution and the solution was subjected to HP-20 column chromatography using 80% aqueous acetonitrile as an eluent. The fractions containing the desired product were concentrated under the reduced pressure and freeze-dried to give 0.21g of the desired compound (78%).

The NMR spectra of the desired compound were the same as those of the compound prepared in Example 12.

Example 72

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-amino-1,2,4-triazol-4-ium)methyl]-ceph-3-em-4-carboxylate

- 5 By following the procedure in Example 71 except that 0.34g(4mmol) of 1-amino-1,2,4-triazole was employed in place of 4-amino-1,2,4-triazole, there was obtained 0.63g of the desired compound(44%).

The NMR spectra of the desired compound were the same as those of the compound prepared in Example 13.

10

Example 73

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-aminotetrazol-4-ium)methyl]-ceph-3-em-4-carboxylate

- 15 By following the procedure in Example 71 except that 0.34g(4mmol) of 1-aminotetrazole was employed in place of 4-amino-1,2,4-triazole, there was obtained 0.6g of the desired compound(41%).

The NMR spectra of the desired compound were the same as those of the compound prepared in Example 16.

20

Example 74

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(2-amino-1,2,3,4-tetrahydroisoquinolin-2-ium)methyl]-ceph-3-em-4-carboxylate

- 25 In 6ml of dry dichloromethane was suspended 0.59g(1.3mmol) of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylic acid, 1.21ml(6.5mmol) of N,O-

bis(trimethylsilyl) trifluoroacetamide was added thereto under gaseous nitrogen atmosphere and the mixture was stirred at room temperature for 1 hour. 0.5ml(3.5mmol) of iodotrimethylsilane was added, and the resulting mixture was stirred at room temperature for 30 min. and concentrated under the reduced pressure. The residue was dissolved in 6ml of dry acetonitrile, 0.9ml of dry tetrahydrofuran was added thereto and the mixture was stirred for 10 min. 0.27g(2mmol) of 2-amino-1,2,3,4-tetrahydroisoquinoline and 1ml of dry dichloromethane were added and the reaction mixture was stirred at room temperature for 3 hours. After completion of reaction, 0.3ml of water was added under cooling. The resulting precipitate was filtered, washed with a mixed solvent of acetonitrile and diethyl ether, dried and suspended in a small amount of water, after which the pH was adjusted to 5~6 with saturated sodium bicarbonate solution. Then, purification was effected by HP-20 (Mitsubishi) column chromatography using 8% aqueous ethanol as an eluent. The fractions containing the desired product were concentrated under the reduced pressure and freeze-dried to give 268mg of the desired compound(38%).

The NMR spectra of the desired compound were the same as those of the compound prepared in Example 5.

Example 75

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-aminoindoliniummethyl)-ceph-3-em-4-carboxylate

By following the procedure in Example 74 except that 0.27g(2mmol) of 1-aminoindoline was employed in place of 2-amino-1,2,3,4-tetrahydro-

isoquinoline, there was obtained 0.23g of the desired compound(34%).

The NMR spectra of the desired compound were the same as those of the compound prepared in Example 6.

5 Example 76

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-3-em-4-carboxylate

In 6ml of dry dichloromethane was suspended 0.59g(1.3mmol) of (6R, 10 7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylic acid, 1.21ml(6.5mmol) of N,O-bis(trimethylsilyl) trifluoroacetamide was added thereto under gaseous nitrogen atmosphere and the mixture was stirred at room temperature for 1 hour. 0.5ml(3.5mmol) of iodotrimethylsilane was added, and the 15 reaction mixture was stirred at room temperature for 30 min and concentrated under the reduced pressure. The residue was dissolved in 6ml of dry acetonitrile, 0.9ml of dry tetrahydrofuran was added thereto and the mixture was stirred for 10 min. 0.296g(2.2mmol) of 1-amino-benzotriazole and 3ml of dry dichloromethane were added and the reaction 20 mixture was stirred at room temperature for 5 hours. After completion of reaction, 0.3ml of water was added under cooling. The resulting precipitate was filtered, washed with a mixed solvent of acetonitrile and diethyl ether, dried, suspended in a small amount of water and the pH was adjusted to 4~4.5 with saturated sodium bicarbonate 25 solution. Purification was effected by HP-20 (Mitsubishi) column chromatography using 15% aqueous acetonitrile as an eluent. The fractions containing the desired product were concentrated under the

reduced pressure and freeze-dried to give 255mg of the desired compound (37%).

The NMR spectra of the desired compound were the same as those of the compound prepared in Example 18.

5

Example 77

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-aminobenzimidazol-3-ium)methyl]-ceph-3-en-4-carboxylate

10 By following the procedure in Example 76 except that 0.29g(2.2mmol) of 1-aminobenzimidazole was employed in place of 1-aminobenzotriazole, there was obtained 0.29g of the desired compound(42%).

The NMR spectra of the desired compound were the same as those of the compound prepared in Example 19.

15

Example 78

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-amino-1,4,5,6-tetrahydropyrimidin-3-ium)methyl]-ceph-3-en-4-carboxylate

20 By following the procedure in Example 76 except that 0.22g(2.2mmol) of 1-amino-1,4,5,6-tetrahydropyrimidine was employed in place of 1-aminobenzotriazole, there was obtained 0.2g of the desired compound (31%).

25 The NMR spectra of the desired compound were the same as those of the compound prepared in Example 21.

Preparation Example 7

Synthesis of 4-methoxybenzyl 7 β -(2-hydroxybenzylideneamino)
-3-chloromethyl-ceph-3-em-4-carboxylate

In 50ml of methanol was dissolved 4.05g(10mmol) of 4-methoxybenzyl
5 7 β -amino-3-chloromethyl-ceph-3-em-4-carboxylate hydrochloride, and
1.28ml(12mmol) of salicylaldehyde and 1.39ml(10mmol) of triethylamine
were added thereto. The reaction mixture was stirred for 5 hours. The
resulting precipitate was filtered, washed with 50ml of methanol and
dried to give 4.26g of the desired compound(90%).

10 NMR (DMSO-d₆, δ)

3.7 (d, 2H, C-2), 3.77 (s, 3H, OCH₃)

4.53 (s, 2H), 5.22 (s, 2H)

5.35 (d, 1H), 5.66 (d, 1H), 6.85~7.58 (m, 8H, phenyl)

8.75 (s, 1H)

15

Preparation Example 8

Synthesis of 4-methoxybenzyl 7 β -(2-hydroxybenzylideneamino)
-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-3-em-4-carboxylate
iodide

20 To 50ml of acetone was added 4.73g(10mmol) of 4-methoxybenzyl 7 β -
(2-hydroxybenzylideneamino)-3-chloromethyl-ceph-3-em-4-carboxylate
prepared in Preparation Example 7 and 1.6g(10.7mmol) of sodium iodide
was added thereto. The mixture was stirred for 3 hours in the
darkness, concentrated under the reduced pressure to remove acetone.
25 The concentrate was dissolved in acetonitrile(4.8ml), and 1.07ml(10mmol)
of salicylaldehyde and 4.3g(30mmol) of 1-aminobenzotriazole were added
thereto and the mixture was stirred at 20~25°C for 24 hours. To the

reaction solution was added 50ml of acetone and the insoluble was filtered off. A mixture of diisopropyl ether (500ml) and diethyl ether (500ml) was added to the filtrate. The resulting precipitate was filtered and dried to give 6.28g of the desired compound (90%).

5 NMR (DMSO- d_6 , δ)

3.76 (s, 5H, OCH₃, C-2), 5.27 (s, 2H)

5.43 (d, 1H, C-6), 5.82 (d, 1H, C-7)

5.9 (q, 2H, C-3), 6.8~7.6 (m, 8H, phenyl)

8.0~8.33 (m, 4H), 8.83 (s, 1H)

10

Preparation Example 9

Synthesis of 4-methoxybenzyl 7 β -amino-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-3-em-4-carboxylate iodide

To 25ml of acetonitrile was added 7g(10mmol) of 4-methoxybenzyl 7 β -(2-hydroxybenzylideneamino)-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-3-em-4-carboxylate iodide prepared in the above Preparation Example 8, and 10ml of conc. hydrochloric acid was slowly added thereto at 0~5°C. To the reaction mixture was added 100ml of isopropyl alcohol, and the resulting precipitate was filtered and dried to give 5g of the
15
20 desired compound (80%).

NMR (DMSO- d_6 , δ)

3.74 (s, 5H, OCH₃, C-2), 5.23 (bs, 2H)

5.4 (s, 2H, C-6, C-7), 5.95 (q, 2H, C-3)

6.8~7.3 (m, 4H, phenyl), 8.0~8.27 (m, 4H)

25

Preparation Example 10

Synthesis of 4-methoxybenzyl (6R,7R)-7-[(Z)-2-(2-aminothiazol-

4-yl)-2-methoxyiminoacetamido]-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-3-em-4-carboxylate iodide

To a mixture of phosphorus oxychloride (1.21ml, 12mmol) and ethyl acetate (40ml) was added 2.21g(11mmol) of (Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetic acid and the mixture was stirred at 2~6°C for 30 min. 1.12ml(12mmol) of further phosphorus oxychloride was added and the mixture was stirred at 4~6°C for 30 min. 0.93ml(12mmol) of N,N-dimethylformamide was added and the mixture was stirred at the same temperature for 1 hour. Thus obtained solution was added to a solution of 6.31g(10mmol) of 4-methoxybenzyl 7 β -amino-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-3-em-4-carboxylate iodide prepared in Preparation Example 9 and 14.8ml(60mmol) of N,O-bis(trimethylsilyl)acetamide in 40ml of ethyl acetate at -10~-5°C and the mixture was stirred at -5°C for 30 min. To the reaction solution were added 100ml of ethyl acetate and 50ml of water and the pH was adjusted to 6~7 with sodium bicarbonate. The organic layer was dried over anhydrous magnesium sulfate, concentrated under the reduced pressure and 300ml of diisopropyl ether was added. The resulting precipitate was filtered and dried to give 5.8g of the desired compound (75%).

20 NMR (DMSO-d₆, δ)

3.28~3.85 (m, 5H, C-2, OCH₃), 3.9 (s, 3H, OCH₃)

5.1 (d, 1H), 5.27 (bs, 2H), 5.6~6.0 (m, 3H)

6.8~7.3 (m, 5H, phenyl, thiazole-H)

8.0~8.3 (m, 4H)

25

Example 79

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-

-methoxyiminoacetamido]-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-3-em-4-carboxylate

To a mixture of trifluoroacetic acid (15ml) and anisole (7.5ml) was added 7.8g (10mmol) of 4-methoxybenzyl (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-3-em-4-carboxylate iodide prepared in Preparation Example 10 and the mixture was stirred at 35°C for 4 hours. The reaction solution was concentrated under the reduced pressure and added to 500ml of diethyl ether. The resulting precipitate was filtered, water was added thereto and the pH was adjusted to 4~4.5. Purification was effected by HP-20 column chromatography using 12% aqueous ethanol as an eluent. The fractions containing the desired product was concentrated under the reduced pressure and freeze-dried to give 3.9g of the desired compound (75%).

The NMR spectra of the desired compound were the same as those of the compound prepared in Example 18.

Preparation Example 11

Synthesis of 7 β -amino-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-3-em-4-carboxylate

In a mixture of trifluoroacetic acid (15ml) and anisole (7.5ml) was dissolved 6.3g(10mmol) of 4-methoxybenzyl 7 β -amino-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-3-em-4-carboxylate iodide and the solution was stirred at 30~35°C for 4 hours. The reaction solution was concentrated under the reduced pressure, 500ml of diisopropyl ether was added, and the resulting precipitate was filtered and dried. To the solid was added water and purification was effected by HP-20 column.

chromatography using 15% aqueous ethanol as an eluent. The fractions containing the desired product were concentrated under the reduced pressure and freeze-dried to give 2.6g of the desired compound(75%).

NMR (DMSO-d₆, δ)

- 5 3.7 (m, 2H, C-2), 5.2 (m, 2H, C-6, C-7)
 6.0 (q, 2H, C-3), 7.9~8.4 (m, 4H)

Example 80

- 10 Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-3-em-4-carboxylate

15 To a mixture of phosphorus oxychloride (1.12ml, 12mmol) and ethyl acetate(40ml) was added 2.21g(11mmol) of (Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetic acid and the mixture was stirred at 2~6°C for 30 min. Further 1.21ml(12mmol) of phosphorus oxychloride was added and the resulting mixture was stirred at 4~6°C for 30 min. To the reaction solution was added 0.93ml(12mmol) of N,N-dimethylformamide and the mixture was stirred at the same temperature for 1 hour.

- 20 In 40ml of ethyl acetate were dissolved 3.5g(10mmol) of 7 β -amino-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-3-em-4-carboxylate prepared in Preparation Example 11 and 14.8ml(60mmol) of N,O-bis(trimethylsilyl)acetamide, the solution prepared in the above was slowly added thereto at -10~-5°C and the mixture was stirred at -5°C for 30 min. After confirming the completion of reaction, 10ml of methanol was added and
25 the solution was concentrated under the reduced pressure. To the residue was added water, the pH was adjusted to 4~4.5 and purification was effected by HP-20 column chromatography using 12% aqueous ethanol as

an eluent. The fractions containing the desired product were concentrated under the reduced pressure and freeze-dried to give 3.7g of the desired compound(70%).

The NMR spectra of the desired compound were the same as those of the compound obtained in Example 18.

Preparation Example 12

Synthesis of 4-methoxybenzyl (6R,7R)-7-[(Z)-2-(2-tritylaminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-3-em-4-carboxylate iodide

In 15ml of dichloromethane was suspended 0.63g(3mmol) of phosphorus pentachloride and the suspension was cooled to -30°C. 1.2g(2.5mmol) of (Z)-2-(2-tritylaminothiazol-4-yl)-2-methoxyiminoacetic acid hydrochloride was added slowly and the mixture was stirred at -20~-15°C for 2 hours. 1.63g(2.75mmol) of 4-methoxybenzyl 7 β -amino-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-3-em-4-carboxylate iodide obtained in the above Preparation Example 9 was added to 30ml of acetonitrile, 2.22ml(9mmol) of N,O-bis(trimethylsilyl) acetamide was added thereto and the mixture was stirred at 10~15°C for 1.5 hours. To this reaction solution was slowly added the solution obtained in the above at -30~-25°C, the mixture was stirred at -20~-15°C for 1.5 hours and 20ml of water and 40ml of ethyl acetate were added. The organic layer was washed with saturated sodium bicarbonate solution and with saturated brine. The organic layer was dried over anhydrous sodium sulfate and the solid was filtered off. The filtrate was concentrated under the reduced pressure, and dichloromethane and diethyl ether were added.

The resulting precipitate was filtered and dried to give 1.68g of the desired compound(60%).

NMR (DMSO-d₆, δ)

- 3.6~3.8 (m, 2H, C-2), 3.83 (s, 3H)
5 3.87 (s, 3H), 5.13 (d, 1H), 5.3 (bs, 2H)
5.8~6.1 (m, 3H), 6.87 (s, 1H, thiazole-H)
6.9~7.5 (m, 19H), 7.6~7.9 (m, 4H)

Example 81

- 10 Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-aminobenzotriazol-3-ium) methyl]-ceph-3-en-4-carboxylate

- To 1.0g(1mmol) of 4-methoxybenzyl (6R,7R)-7-[(Z)-2-(2-tritylaminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-aminobenzotriazol-3-ium) methyl]-ceph-3-en-4-carboxylate iodide prepared in the above Preparation
15 Example 12 were added 2ml of trifluoroacetic acid and 1ml of anisole, the mixture was stirred at 15~20°C for 2 hours and concentrated under the reduced pressure to remove trifluoroacetic acid. Diisopropyl ether was added, the resulting precipitate was filtered and dissolved in 5ml
20 of methanol. The insoluble was filtered off and the filtrate was concentrated under the reduced pressure. A small amount of water was added to the residue, the pH was adjusted to 4~4.5 and purification was effected by HP-20 column chromatography using 12% aqueous ethanol as an eluent. The fractions containing the desired compound were
25 concentrated under the reduced pressure and freeze-dried to give 0.4g of the desired compound(75%).

The NMR spectra of the desired compound were the same as those of

the compound obtained in Example 18.

Preparation Example 13

Synthesis of diphenylmethyl (6R,7R)-7-[(Z)-2-(2-tritylaminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(4-amino-1,2,4-triazol-2-ium)methyl]-ceph-3-em-4-carboxylate iodide

By following the procedure in Preparation Example 12 except that 1.62g(2.75mmol) of diphenylmethyl 7 β -amino-3-[(4-amino-1,2,4-triazol-2-ium)methyl]-ceph-3-em-4-carboxylate iodide was employed in place of 4-methoxybenzyl 7 β -amino-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-3-em-4-carboxylate iodide, there was obtained 1.78g of the desired compound (70%).

NMR (DMSO-d₆, δ)

3.4~3.6 (m, 2H), 3.78 (s, 3H)
5.2 (d, 1H), 5.5~5.9 (m, 3H)
6.8 (s, 1H), 7.1 (s, 1H)
7.1~7.6 (m, 25H), 8.5, 9.3 (s, s, 2H)

Example 82

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(4-amino-1,2,4-triazol-2-ium)methyl]-ceph-3-em-4-carboxylate

By following the procedure in Example 81 except that 1.0g(1mmol) of the compound prepared in the above Preparation Example 13 was employed, there was obtained 0.37g of the desired compound(78%).

The NMR spectra of the desired compound were the same as those of the compound obtained in Example 12.

Example 83

Synthesis of (6R,7R)-7-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-carboxymethoxyiminoacetamido]-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-3-em-4-carboxylate

5 By following the procedure in Example 60 except that 0.5g(1mmol) of (6R,7R)-7-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-carboxymethoxyiminoacetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylic acid was employed in place of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylic acid, there was
10 obtained 0.15g of the desired compound(26%).

MS(FAB, M+1) = 575

NMR(DMSO-d₆ + 20% DCl, δ)

3.8~4.0 (m, 2H), 4.73 (s, 2H)

5.1~5.52 (m, 3H), 5.82 (d, 1H)

15 7.5~8.2 (m, 4H)

Example 84

Synthesis of (6R,7R)-7-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(2-carboxyprop-2-oxymino)acetamido]-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-3-em-4-carboxylate

20 By following the procedure in Example 49 except that 0.57g (1.09mmol) of (6R,7R)-7-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(2-carboxyprop-2-oxymino)acetamido]-3-acetoxymethyl-ceph-3-em-4-carboxylic acid was employed, there was obtained 0.12g of the desired compound
25 (20%).

MS(FAB, M+1) = 603

NMR(DMSO-d₆ + 20% DCl, δ)

1.3 (d, 6H), 3.86~4.1 (m, 2H)

5.05~5.55 (m, 3H), 5.8 (d, 1H)

7.5~8.1 (m, 4H)

5 Example 85

Synthesis of (6R,7R)-7-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-3-em-4-carboxylate

In a mixture of acetonitrile (1ml) and water (1.5ml) was dissolved
10 0.67g(5mmol) of lithium iodide and the solution was heated to 65~67°C.
0.24g(1.8mmol) of 1-aminobenzotriazole and 0.46g(1mmol) of (6R,7R)-7-
[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-
acetoxymethyl-ceph-3-em-4-carboxylic acid were added and the mixture was
stirred at 70°C for 1 hour while adjusting its pH to 6.8~7.1. After
15 completion of reaction, the reaction solution was cooled to room
temperature and stirred for 30 min while adjusting the pH to 1~1.5 with
3N hydrochloric acid. The insoluble was filtered off, the filtrate was
concentrated under the reduced pressure and subjected to column
chromatography over aluminium oxide and over silica gel using 80%
20 aqueous acetonitrile as an eluent. The fractions were concentrated
under the reduced pressure, dissolved in a small amount of water and
purified by HP-20(Mitsubishi) column chromatography using 15% aqueous
ethanol as an eluent. The fractions containing the desired product
were concentrated under the reduced pressure and freeze-dried to give
25 0.14g of the desired compound in a pale yellowish white amorphous form
(26.4%).

MS(FAB, M+1) = 531

NMR(DMSO-d₆ + 20% DCl, δ)

3.8~4.0 (m, 2H), 4.05 (s, 3H)

5.1~5.6 (m, 3H), 5.85 (d, 1H)

7.6~8.1 (m, 4H)

5

Example 86

Synthesis of (6R,7R)-7-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[(1-aminobenzimidazol-3-ium)methyl]-ceph-3-em-4-carboxylate

10 By following the procedure in Example 85 except that 0.24g(1.8mmol) of 1-aminobenzimidazole was employed in place of 1-aminobenzotriazole, there was obtained 0.13g of the desired compound (24%).

MS(FAB, M+1) = 530

NMR(DMSO-d₆, δ)

15 3.3~3.7 (m, 2H), 3.8 (s, 3H)

5.05 (d, 1H), 5.4~5.85 (m, 3H)

7.5~8.5 (m, 4H), 10.1 (s, 1H)

Example 87

20 Synthesis of (6R,7R)-7-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[(1-amino-1,2,4-triazol-4-ium)methyl]-ceph-3-em-4-carboxylate

By following the procedure in Example 85 except that 0.15g(1.8mmol) of 1-amino-1,2,4-triazole was employed in place of 1-aminobenzotriazole, there was obtained 0.14g of the desired compound (29%).

25

MS(FAB, M+1) = 481

NMR(DMSO-d₆ + 20% DCl, δ)

3.25~3.7 (m, 2H), 3.8 (s, 3H)

5.1~5.3 (m, 3H), 5.6 (d, 1H)

8.7, 9.7 (s,s, 2H)

5 Example 88

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-3-em-4-carboxylate sulfate

In 4ml of water was dissolved 0.5g(0.95mmol) of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-3-em-4-carboxylate prepared in Example 18, the solution was cooled to 5°C and the pH was adjusted to 1~1.5 with 3N sulfuric acid. After stirring at the same temperature for 1 hour, 10ml of isopropyl alcohol was added and the mixture was stirred at 0~5°C for 4 hours. The resulting precipitate was filtered, washed with isopropyl alcohol and diethyl ether and dried to give 0.54g of the desired compound in a form of white crystalline solid (91%).

m.p. = 176°C ~ (decomp.)

MS(FAB, M+1) = 628

20 NMR (DMSO-d₆, δ)

3.51 (q, 2H, C-2), 3.83 (s, 3H, OCH₃)

5.2 (d, 1H), 5.4~5.94 (m, 3H)

6.74 (s, 1H, thiazole-H)

8.02~8.52 (m, 6H), 9.6 (d, 1H)

25

Example 89

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-

methoxyiminoacetamido]-3-[(4-amino-1,2,4-triazol-2-ium)
methyl]-ceph-3-em-4-carboxylate sulfate

By following the procedure in Example 88 except that 0.2g(0.42mmol)
of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-
5 [(4-amino-1,2,4-triazol-2-ium)methyl]-ceph-3-em-4-carboxylate prepared
in Example 12 was employed in place of (6R,7R)-7[(Z)-2-(2-aminothiazol-
4-yl)-2-methoxyiminoacetamido]-3-[(1-aminobenzotriazol-3-ium)methyl]-
ceph-3-em-4-carboxylate, there was obtained 0.22g of the desired
compound (91.3%).

10 NMR (DMSO-d₆, δ)

3.5 (m, 2H, C-2), 3.83 (s, 3H, OCH₃)

5.1 (d, 1H, C-6), 5.4~5.85 (m, 3H, C-7, C-3)

6.75 (s, 1H, thiazole-H), 8.76, 9.81 (s, s, 2H, triazole)

15 Example 90

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-
methoxyiminoacetamido]-3-[(1-aminobenzimidazol-3-ium)
methyl]-ceph-3-em-4-carboxylate sulfate

By following the procedure in Example 88 except that 0.25g(0.47mmol)
20 of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-
[(1-aminobenzimidazol-3-ium)methyl]-ceph-3-em-4-carboxylate Prepared in
Example 19 was employed in place of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-
yl)-2-methoxyiminoacetamido]-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-
3-em-4-carboxylate, there was obtained 0.26g of the desired compound
25 (88%).

NMR (DMSO-d₆, δ)

3.3~3.6 (m, 2H, C-2), 3.81 (s, 3H, OCH₃)

107

5.08 (d, 1H, C-6), 5.5~5.9 (m, 3H, C-7, C-3)
6.76 (s, 1H, thiazole-H), 7.5~8.4 (m, 4H, phenyl)
10.1 (s, 1H, imidazole)

5 Example 91

Synthesis of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-3-em-4-carboxylate maleate

In 1.5ml of water was dissolved 0.15g(0.28mmol) of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-3-em-4-carboxylate prepared in Example 18, the solution was cooled to 5~10°C, 0.034g(0.29mmol) of maleic acid was added thereto and the mixture was stirred at 5°C for 2 hours. A mixture of isopropyl alcohol (12ml) and diethyl ether(3ml) was added and the resulting mixture was stirred at 0~5°C for 5 hours. The resulting precipitate was filtered, washed with diethyl ether and dried to give 0.15g of the desired compound in a form of white crystalline solid (82%).

m.p. = 136°C ~ (decomp.)

20 NMR (DMSO-d₆, δ)

3.55 (q, 2H, C-2), 3.85 (s, 3H, OCH₃)

5.19 (d, 1H), 5.4~5.96 (m, 3H)

6.06 (s, 2H), 6.75 (s, 1H, thiazole-H), 8.03~8.48 (m, 6H)

25

Example 92

Synthesis of (6R,7R)-7-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-3-em-4-carboxylate sulfate

5 By following the procedure in Example 88 except that 0.5g(0.94mmol) of (6R,7R)-7-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-3-em-4-carboxylate prepared in Example 85 was employed in place of (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-aminobenzotriazol-3-ium)methyl]-ceph-3-em-4-carboxylate, there was obtained 0.51g of the
10 desired compound (86%).

NMR (DMSO-d₆, δ)

3.75~4.0 (m, 2H), 4.03 (s, 3H)

5.15 (d, 1H), 5.45~5.9 (m, 3H)

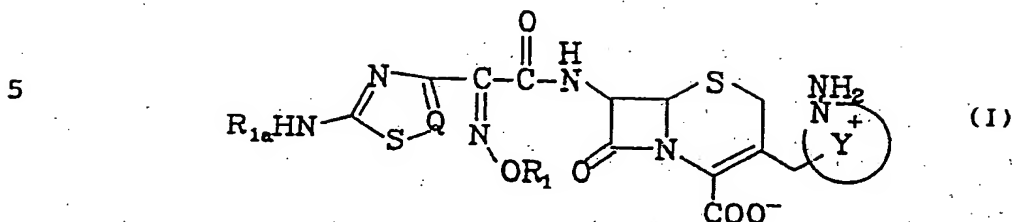
15 7.7~8.05 (m, 4H)

20

25

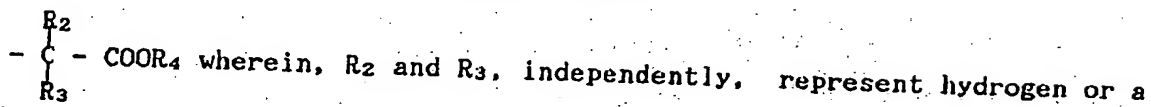
What we claim is:

1. A compound of the formula (I)



wherein,

- 10 R_1 represents a $C_1 \sim C_4$ alkyl group or

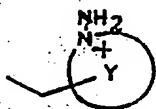


$C_1 \sim C_3$ alkyl group and R_4 represents hydrogen or a $C_1 \sim C_4$ alkyl group;

- 15 R_{1a} represents hydrogen or an amino-protecting group;

Q represents CH or N; and

the formula

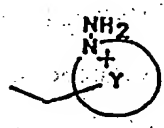


represents a saturated or unsaturated

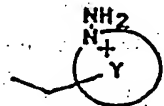
- 20 heterocyclic group which contains 1 to 4 nitrogen atoms of which one is substituted with an amino group to form quaternary ammonium, and oxygen or sulfur, or a fused heterocyclic group thereof formed together with a substituted or unsubstituted benzene or an optional heterocyclic group, and is the group selected from the group comprising:

- 25 1-aminopyrrolidinium methyl, 1-aminopiperidinium methyl,
(4-aminomorpholin-4-ium)methyl,
(1-amino-1,2,3,6-tetrahydropyridinium)methyl,
(1-amino-3-pyrrolin-1-ium)methyl,

- 1-aminoindolinium methyl,
 1-aminopyrrolidium methyl,
 1-aminoindolium methyl,
 (1-amino-4-hydroxypiperidinium)methyl,
 5 (2-amino-1,2,3,4-tetrahydroisoquinolin-2-ium)methyl,
 (1-amino-1-methyl-4-piperazinium)methyl,
 (4-amino-1,2,4-triazol-2-ium)methyl,
 (1-amino-1,2,3-triazol-3-ium)methyl,
 (1-amino-1,2,4-triazol-4-ium)methyl,
 10 (1-aminobenzotriazol-3-ium)methyl,
 (1-aminobenzimidazol-3-ium)methyl,
 (1-aminoimidazol-3-ium)methyl,
 (1-aminopyrazol-2-ium)methyl,
 (1-aminotetrazol-4-ium)methyl,
 15 (1-amino-1,4,5,6-tetrahydropyrimidin-3-ium)methyl and
 (1-aminoindazol-2-ium)methyl,
 and a pharmaceutically acceptable salt thereof.
2. The compound according to Claim 1, wherein R₁ is methyl, -CH₂COOH

20 or $\begin{array}{c} \text{CH}_3 \\ | \\ -\text{C}-\text{COOH} \\ | \\ \text{CH}_3 \end{array}$; R_{1a} is hydrogen; Q is CH or N; and  is 1-aminopyrrolidinium methyl, and a pharmaceutically acceptable salt thereof.

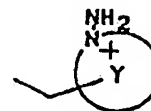
3. The compound according to Claim 1, wherein R₁ is methyl, -CH₂COOH

25 or $\begin{array}{c} \text{CH}_3 \\ | \\ -\text{C}-\text{COOH} \\ | \\ \text{CH}_3 \end{array}$; R_{1a} is hydrogen; Q is CH or N; and  is (2-amino-1,2,3,4-tetrahydroisoquinolin-2-ium)methyl, and a pharmaceuti-

cally acceptable salt thereof.

4. The compound according to Claim 1, wherein R_1 is methyl, $-\text{CH}_2\text{COOH}$

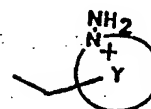
or $-\text{C}(\text{CH}_3)_2 - \text{COOH}$; R_{1a} is hydrogen; Q is CH or N; and



5 is (1-amino-1-methyl-4-piperazinium)methyl, and a pharmaceutically acceptable salt thereof.

5. The compound according to Claim 1, wherein R_1 is methyl, $-\text{CH}_2\text{COOH}$

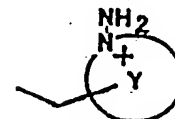
or $-\text{C}(\text{CH}_3)_2 - \text{COOH}$; R_{1a} is hydrogen; Q is CH or N; and



10 is (4-amino-1,2,4-triazol-2-ium)methyl, and a pharmaceutically acceptable salt thereof.

6. The compound according to Claim 1, wherein R_1 is methyl, $-\text{CH}_2\text{COOH}$

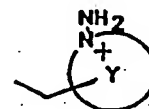
15 or $-\text{C}(\text{CH}_3)_2 - \text{COOH}$; R_{1a} is hydrogen; Q is CH or N; and



is (1-amino-1,2,3-triazol-3-ium)methyl, and a pharmaceutically acceptable salt thereof.

7. The compound according to Claim 1, wherein R_1 is methyl, $-\text{CH}_2\text{COOH}$

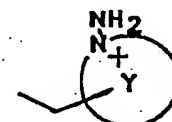
20 or $-\text{C}(\text{CH}_3)_2 - \text{COOH}$; R_{1a} is hydrogen; Q is CH or N; and



is (1-amino-1,2,4-triazol-4-ium)methyl, and a pharmaceutically acceptable salt thereof.

8. The compound according to Claim 1, wherein R_1 is methyl, $-\text{CH}_2\text{COOH}$

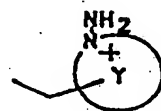
25 or $-\text{C}(\text{CH}_3)_2 - \text{COOH}$; R_{1a} is hydrogen; Q is CH or N; and



is (1-aminobenzotriazol-3-ium)methyl, and a pharmaceutically acceptable salt thereof.

9. The compound according Claim 1, wherein, R_1 is methyl, $-\text{CH}_2\text{COOH}$ or

5 $-\text{C}(\text{CH}_3)_2\text{COOH}$; R_{1a} is hydrogen; Q is CH and N; and

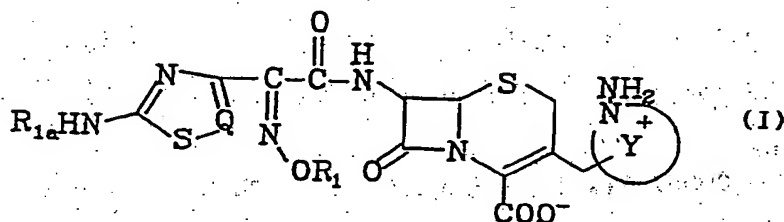


is

(1-aminobenzimidazol-3-ium)methyl, and a pharmaceutically acceptable salt thereof.

10. The compound according to any one of Claims 1 to 9, the pharmaceutically acceptable salt is hydrochloride, sulfate or maleate.

11. A process for preparing the compounds of the formula(I);



wherein,

R_1 represents a $\text{C}_1 \sim \text{C}_4$ alkyl group or

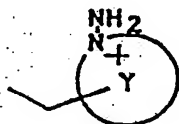
20 $-\text{C}(\text{R}_2)(\text{R}_3)\text{COOR}_4$ wherein, R_2 and R_3 , independently, represent hydrogen or a

$\text{C}_1 \sim \text{C}_3$ alkyl group and R_4 represents hydrogen or a $\text{C}_1 \sim \text{C}_4$ alkyl group;

R_{1a} represents hydrogen or an amino-protecting group;

Q represents CH or N; and

25 the formula



represents a saturated or unsaturated

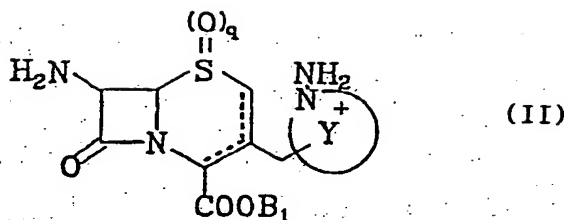
heterocyclic group which contains 1 to 4 nitrogen atoms of which one is substituted with an amino group to form quaternary ammonium, and oxygen or sulfur, or a fused heterocyclic group thereof formed together with a substituted or unsubstituted benzene or an optional heterocyclic group, and is the group selected from the group comprising:

- 1-aminopyrrolidinium methyl, 1-aminopiperidinium methyl,
- (4-aminomorpholin-4-ium)methyl,
- (1-amino-1,2,3,6-tetrahydropyridinium)methyl,
- (1-amino-3-pyrrolin-1-ium)methyl,
- 10 1-aminoindolinium methyl,
- 1-aminopyrrolium methyl,
- 1-aminoindolium methyl,
- (1-amino-4-hydroxypiperidinium)methyl,
- (2-amino-1,2,3,4-tetrahydroisoquinolin-2-ium)methyl,
- 15 (1-amino-1-methyl-4-piperazinium)methyl,
- (4-amino-1,2,4-triazol-2-ium)methyl,
- (1-amino-1,2,3-triazol-3-ium)methyl,
- (1-amino-1,2,4-triazol-4-ium)methyl,
- (1-aminobenzotriazol-3-ium)methyl,
- 20 (1-aminobenzimidazol-3-ium)methyl,
- (1-aminoimidazol-3-ium)methyl,
- (1-aminopyrazol-2-ium)methyl,
- (1-aminotetrazol-4-ium)methyl,
- (1-amino-1,4,5,6-tetrahydropyrimidin-3-ium)methyl and
- 25 (1-aminoindazol-2-ium)methyl,

or a pharmaceutically acceptable salt thereof, which comprises reacting the compounds of the formula (II)

114

5



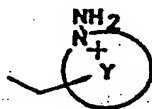
wherein,

B₁ represents hydrogen or a carboxyl-protecting group;

10 q is an integer of 0 or 1;

the dotted line means ceph-2-em or ceph-3-em compound; and

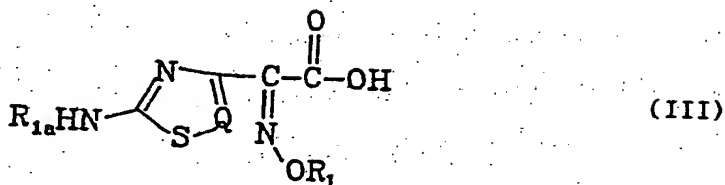
the formula



is the same as defined

15 above, with the compounds of the formula (III);

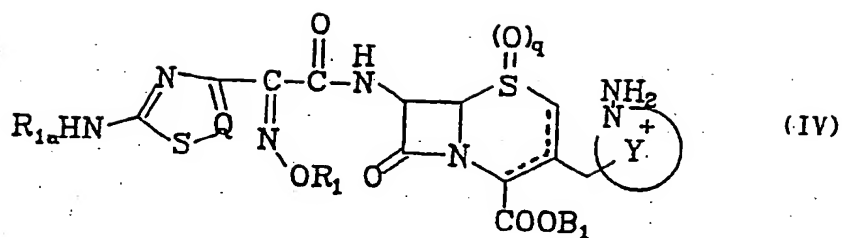
20



wherein,

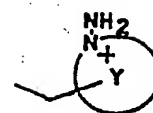
25 R₁, R_{1a} and Q are the same as defined above, or an acylated derivative thereof to give the compounds of the formula (IV);

115



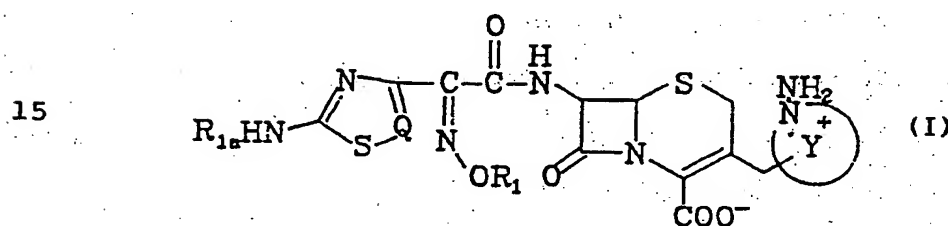
wherein,

10 R_1 , R_{1a} , B_1 , Q , q , the dotted line and the formula



are the same as defined above, and removing the protecting groups.

12. A process for preparing the compounds of the formula(I);



wherein,

20 R_1 represents a $C_1 \sim C_4$ alkyl group or

$\begin{array}{c} R_2 \\ | \\ -C- \\ | \\ R_3 \end{array} - COOR_4$ wherein, R_2 and R_3 , independently, represent hydrogen or a

$C_1 \sim C_3$ alkyl group and R_4 represents hydrogen or a $C_1 \sim C_4$ alkyl group;

R_{1a} represents hydrogen or an amino-protecting group;

25

Q represents CH or N; and

the formula



represents a saturated or unsaturated

heterocyclic group which contains 1 to 4 nitrogen atoms of which one is substituted with an amino group to form quaternary ammonium, and oxygen or sulfur, or a fused heterocyclic group thereof formed together with a substituted or unsubstituted benzene or an optional heterocyclic group,

5 and is the group selected from the group comprising:

1-aminopyrrolidinium methyl, 1-aminopiperidinium methyl,

(4-aminomorpholin-4-ium)methyl,

(1-amino-1,2,3,6-tetrahydropyridinium)methyl,

(1-amino-3-pyrrolin-1-ium)methyl,

10 1-aminoindolinium methyl,

1-aminopyrrolium methyl,

1-aminoindolium methyl,

(1-amino-4-hydroxypiperidinium)methyl,

(2-amino-1,2,3,4-tetrahydroisoquinolin-2-ium)methyl,

15 (1-amino-1-methyl-4-piperazinium)methyl,

(4-amino-1,2,4-triazol-2-ium)methyl,

(1-amino-1,2,3-triazol-3-ium)methyl,

(1-amino-1,2,4-triazol-4-ium)methyl,

(1-aminobenzotriazol-3-ium)methyl,

20 (1-aminobenzimidazol-3-ium)methyl,

(1-aminoimidazol-3-ium)methyl,

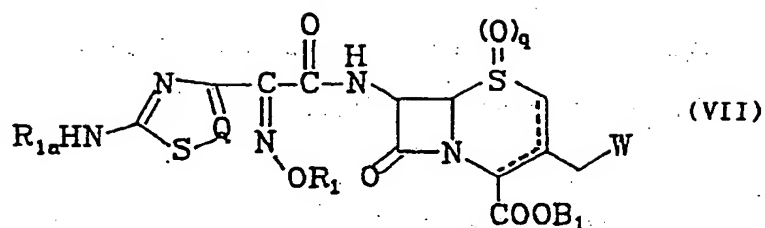
(1-aminopyrazol-2-ium)methyl,

(1-aminotetrazol-4-ium)methyl,

(1-amino-1,4,5,6-tetrahydropyrimidin-3-ium)methyl and

25 (1-aminoindazol-2-ium)methyl,

or a pharmaceutically acceptable salt thereof, which comprises reacting the compounds of the formula (VII);



wherein,

10 W is a residue which may be substituted with a nucleophile and represents an acetoxyl group or a halogen atom such as chlorine, bromine and iodine;

B₁ represents hydrogen or a carboxyl-protecting group;

q is an integer of 0 or 1;

15 the dotted line means ceph-2-em or ceph-3-em compound; and

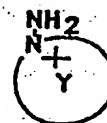
R₁, R_{1a}, and Q are the same as defined above, with the compounds of the formula (IX) or (IXa)

20



(IX)

or



(IXa)

25 which is a saturated or unsaturated heterocyclic group which contains 1 to 4 nitrogen atoms of which one may be substituted with an amino group to form quaternary ammonium, and oxygen or sulfur, or a fused

heterocyclic group thereof formed thereof formed together with a substituted or unsubstituted benzene or an optional heterocyclic group, and is the group selected from the group comprising:

1-aminopyrrolidine, 1-aminopiperidine,

5 4-aminomorpholine,

1-amino-1,2,3,6-tetrahydropyridine,

1-amino-3-pyrroline,

1-aminoindoline,

1-aminopyrrole,

10 1-aminoindole,

1-amino-4-hydroxypiperidine,

2-amino-1,2,3,4-tetrahydroisoquinoline,

1-amino-1-methyl-4-piperazinium,

4-amino-1,2,4-triazole,

15 1-amino-1,2,3-triazole,

1-amino-1,2,4-triazole,

1-aminobenzotriazole,

1-aminobenzimidazole,

1-aminoimidazole,

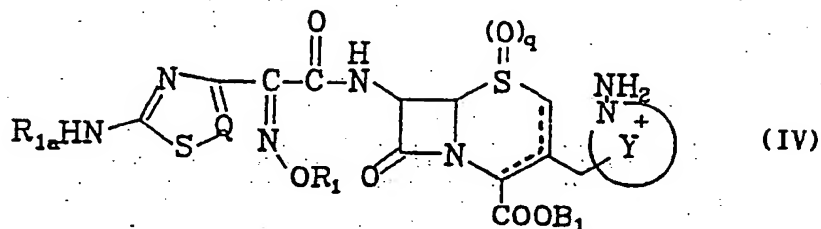
20 1-aminopyrazole,

1-aminotetrazole,

1-amino-1,4,5,6-tetrahydropyrimidine and

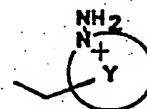
1-aminoindazole

to give the compounds of the formula (IV):



wherein,

10 R_1 , R_{1a} , B_1 , Q , q , the dotted line and the formula



are the same as defined above, and removing the protecting groups.

13. A pharmaceutical composition which comprises a therapeutically effective amount of one or more of the compounds (I) according to Claim
- 15 1 or pharmaceutically acceptable salts thereof as an active ingredient, in association with a pharmaceutically acceptable carrier, excipient or other additive therefor.
14. A compound of the formula (I) as defined in any one of Claims 1 to 9 for use in medicine.
- 20 15. A compound of the formula (I) as defined in any one of Claims 1 to 9 for use as an antibiotic.
16. The use of a compound of the formula (I) as defined in any one of Claims 1 to 9 for the manufacture of a medicament for antibiotic use.
17. Treatment of the diseases caused by bacterial infection which
- 25 comprises administering a therapeutically effective amount of the compounds of formula (I) as defined in Claims 1 to 9 to a subject suffering from such diseases.

INTERNATIONAL SEARCH REPORT

International Application No PCT/KR 91/00012

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl.⁵: C 07 D 501/24; C 07 D 501/38; A 61 K 31/545

II. FIELDS SEARCHED

Minimum Documentation Searched *

Classification System |

Classification Symbols

Int. Cl.⁵: C 07 D 501/00; A 61 K 31/00

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched *

III. DOCUMENTS CONSIDERED TO BE RELEVANT *

Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP, A2, O 249 170 (TAKEDA CHEMICAL INDUSTRIES, LTD.) 16 December 1987 (16.12.87), see claims 1,14,15.	(1,10-16)
A	EP, A2, O 304 858 (TAKEDA CHEMICAL INDUSTRIES, LTD.) 01 March 1989 (01.03.89), see claims 1,7,9.	(1,10-16)
A	EP, A2, O 081 971 (TANABE SEIYAKU CO., LTD.) 22 June 1983 (22.06.83), see the abstract.	(1)

* Special categories of cited documents: ¹⁰

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

03 July 1991 (03.07.91)

Date of Mailing of this International Search Report

11 July 1991 (11.07.91)

International Searching Authority

AUSTRIAN PATENT OFFICE

Signature of Authorized Officer

A. K. K.

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE¹

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 17, because they relate to subject matter not required to be searched by this Authority, namely:

Methods for treatment of the human or animal body by therapy.
Article 17(2) (b) and rule 39.1(iv) PCT

2. ☐ Claim numbers _____, because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers _____, because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING²

This International Searching Authority found multiple inventions in this International application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

Anhang zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

Annex to the International Search Report on International Patent Application No. PCT/KR 91/00012

Annexe au rapport de recherche internationale relatif à la demande de brevet international n°.

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentedokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned International search report. The Austrian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche internationale visé ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l'Office autrichien des brevets.

Im Recherchenbericht angeführtes Patent- dokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
EP-A2- 249170	16-12-87	EP-A3- 249170 US-A - 4921851 JP-A2-63152391	05-07-89 01-05-90 24-06-88
EP-A2- 304858	01-03-89	EP-A3- 304858 US-A - 4942159 JP-A2- 1131185	20-12-89 17-07-90 24-05-89
EP-A2- B1971	22-06-83	EP-A3- B1971 JP-A2-58170790 US-A - 4576938	26-09-84 07-10-83 18-03-86